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54 **Alpha-adrenergic receptor antagonists.**

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WO-A-87/00522
DE-A- 2 306 605
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DescriptionFIELD OF THE INVENTION

5 This invention relates to novel 2-substituted-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine compounds that are α -adrenergic receptor antagonists.

BACKGROUND OF THE INVENTION

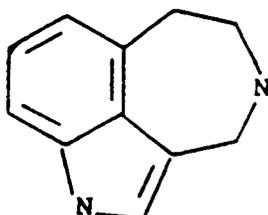
10 The autonomic nervous system is separated into the cholinergic and adrenergic nervous systems. Norepinephrine, the neurotransmitter of the adrenergic nervous system, exerts its activity by interaction with receptors (adrenoceptors) on the effector organs or on the nerve endings. The adrenoceptors are of two primary types: α and β . Based upon selectivity of the receptors for a series of agonists and antagonists, the α adrenoceptors have been subdivided into α_1 and α_2 subtypes.

15 A large amount of experimental evidence now supports the view that the α_2 subtype is a heterogeneous adrenoceptor class. (For a general review see Timmermans and Van Zwieten, *J. Med. Chem.*, 25, 1389 (1982)). Experiments using 6-chloro-9-(3-methyl-2-butenyloxy)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (SK&F 104078) demonstrated that the classical adrenoceptors are heterogeneous and can be divided into SK&F 104078 - insensitive and SK&F 104078 - sensitive α_2 adrenoceptors. The latter variously
20 are referred to as postjunctional α_2 adrenoceptors or, preferably, α_3 adrenoceptors, United States Patent Number 4,683,229, July 28, 1987.

As one of the primary regulators of peripheral vascular tone, α adrenoceptors long have been the targets of efforts to develop agents effective in changing vascular tone for use in treating diseases, such as hypertension, in which alterations in vascular resistance produce therapeutic benefits. Antihypertensive
25 compounds presently in clinical use that function via interaction with α adrenoceptors include methyldopa, clonidine, and prazosin. Efforts to modulate sympathetic tone through interactions with α adrenoceptors have resulted in several compounds that interact somewhat selectively with α_1 or α_2 adrenoceptors. Selective agonists include phenylephrine and methoxamine which preferentially activate α_1 receptors; and clonidine, α -methylnorepinephrine, and tramazoline which preferentially activate α_2 adrenoceptors. Examples of selective α -adrenoceptor antagonists include prazosin which has high selectivity for α_1 adrenoceptors; and the α_2 -selective blockers yohimbine and rauwolscine.

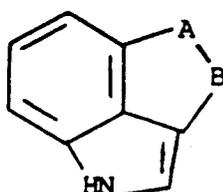
United States Patent No. 4,469,634, dated September 4, 1984, describes allyloxy- and allythio-2,3,4,5-tetrahydro-1H-3-benzazepines useful as intermediates for preparing α_2 adrenoceptor affinity resins and as antihypertensive agents.

35 United States Patents Numbers 3,833,591, 3,904,645, and 3,906,000 disclose substituted compounds of the following base structure:



These compounds are useful as hypoglycemic agents.

PCT Application Number W0 87/00522 describes a series of 4-aminotetrahydrobenz[c,d]indoles and tetrahydroazepino[3,4,5-c,d]indoles having the general formula:



in which A-B is $-\text{CH}_2-\text{CH}(\text{NRR})-\text{CH}_2$ or $-\text{CH}_2-\text{CH}_2-\text{NR}-\text{CH}_2$. These compounds are dopamine agonists useful as hypotensives.

SUMMARY OF THE INVENTION

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The present invention resides in the discovery that various 2-substituted-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine compounds are α -adrenoceptor antagonists or are useful in preparing α -adrenoceptor antagonists. Presently preferred compounds of the invention include:

- 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol;
 10 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde;
 methyl-7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate;
 ethyl-7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate;
 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-[(2-propenyloxy)methyl]thieno[4,3,2-ef][3]benzazepine;
 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine;
 15 7-chloro-3,4,5,6-tetrahydro-2,4-dimethylthieno[4,3,2-ef][3]benzazepine;
 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-ethan-2-ol;
 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-ethan-2-one;
 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxamide;
 N,N-dimethyl-7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]-2-benzazepine carboxamide;
 20 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-(1-methylethyl)thieno[4,3,2-ef][3]benzazepine;
 7-chloro-2-ethyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine;
 7-chloro-2-propyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine; or
 2,7-dichloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine.

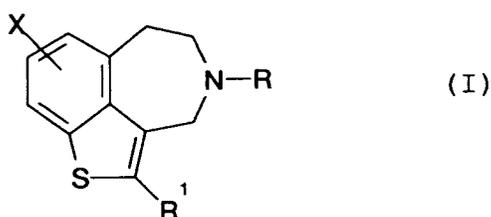
In a further aspect of the invention there are provided methods of antagonizing α adrenoceptors in
 25 mammals, including humans, that comprise administering internally to a subject an effective amount of a 2-substituted-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine compound.

Included in the present invention are pharmaceutical compositions that include compounds useful in the
 method of the invention and a suitable pharmaceutical carrier. Preferably, these compositions are used to
 produce α -adrenoceptor antagonism and contain an effective amount of compounds useful in the methods
 30 of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The presently invented compounds that are α -adrenoceptor antagonists or are useful in preparing α -
 35 adrenoceptor antagonists are represented by the following Formula (I):

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in which:

X is H, Cl, Br, F, I, CF_3 , C_{1-6} alkyl, COR^{10} , CO_2R^{10} , $\text{CONR}^{16}\text{R}^{11}$, CN, NO_2 , $\text{NR}^{12}\text{R}^{13}$, OR^{12} , SC_{1-4} alkyl, $\text{S}(\text{CH}_2)_{0-6}$ aryl, SCF_3 , or any combination thereof of up to three substituents;

R is H, C_{1-6} alkyl, or C_{3-5} alkenyl;

50

R^1 is W, $(\text{CH}_2)_{0-2}\text{CWYZ}$, or C_{3-5} alkenyl, except where the double bond is in the 1-position;

R^{10} is C_{1-6} alkyl or $(\text{CH}_2)_{0-6}$ aryl;

R^{11} and R^{16} independently are H, C_{1-6} alkyl, or $(\text{CH}_2)_{0-6}$ aryl;

R^{12} is H, C_{1-6} alkyl, COR^{14} , or SO_2R^{15} ;

each R^{13} independently is H or C_{1-6} alkyl;

55

R^{14} and R^{15} independently are C_{1-6} alkyl or $(\text{CH}_2)_{0-6}$ aryl;

W is H, NO_2 , C_{1-6} alkyl, $\text{CH}_2\text{CH}_2\text{OH}$, CN, $\text{C}(\text{R}^{13})_2(\text{OR}^2)$, CH_2SR^2 , COR^2 , CO_2R^2 , CONR^3R^4 , $\text{SO}_2\text{NR}^3\text{R}^4$, SO_3R^2 , SO_2R^5 , SOR^5 , SR^5 , $\text{P}(\text{O})(\text{OR}^3)(\text{OR}^4)$, $\text{P}(\text{O})\text{R}^5(\text{OR}^3)$, $\text{P}(\text{O})\text{R}^5\text{R}^6$, $\text{P}(\text{O})(\text{OR}^2)\text{NR}^3\text{R}^4$, $\text{P}(\text{O})(\text{NR}^3\text{R}^4)_2$, $\text{P}(\text{O})\text{R}^5(\text{NR}^3\text{R}^4)$, Cl, Br, F, I, CF_3 , or $(\text{CH}_2)_{0-6}$ aryl;

Y and Z independently are H or C₁₋₆ alkyl;

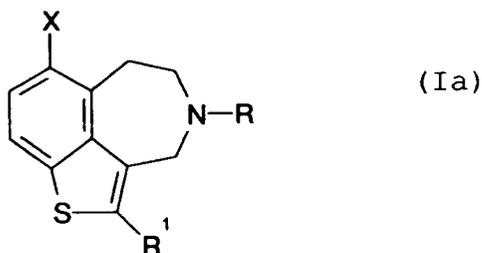
R², R³, and R⁴ independently are H, C₁₋₆ alkyl, C₃₋₅ alkenyl, or (CH₂)₀₋₆ aryl;

R⁵ and R⁶ independently are C₁₋₆ alkyl, C₃₋₅ alkenyl, or (CH₂)₀₋₆ aryl; and

aryl is a phenyl group which is unsubstituted or substituted by C₁₋₆ alkyl, C₁₋₆ alkoxy, halo, CF₃, or CN,
5 or a pharmaceutically acceptable salt thereof.

As used herein C₁₋₆ alkyl means straight or branched alkyl of one to six carbon atoms, and C₃₋₅ alkenyl means a straight or branched chain alkenyl having from 3 to 5 carbon atoms.

Formula (Ia) includes presently preferred Formula (I) compounds:



20 in which:

X is H, Cl, Br, F, I, CF₃, C₁₋₆ alkyl, COR¹⁰, CO₂R¹⁰, CONR¹⁶R¹¹, CN, NO₂, NR¹²R¹³, OR¹², SC₁₋₄ alkyl, S(CH₂)₀₋₆ aryl, or SCF₃;

R is H, C₁₋₆ alkyl, or C₃₋₅ alkenyl;

R¹ is W, (CH₂)₀₋₂ CWYZ, or C₃₋₅ alkenyl, except where the double bond is in the 1-position;

25 R¹⁰ is C₁₋₆ alkyl or (CH₂)₀₋₆ aryl;

R¹¹ and R¹⁶ independently are H, C₁₋₆ alkyl, or (CH₂)₀₋₆ aryl;

R¹² is H, C₁₋₆ alkyl, COR¹⁴, or SO₂R¹⁵;

each R¹³ independently is H or C₁₋₆ alkyl;

R¹⁴ and R¹⁵ independently are C₁₋₆ alkyl or (CH₂)₀₋₆ aryl;

30 W is H, NO₂, C₁₋₆ alkyl, CH₂CH₂OH, CN, C(R¹³)₂(OR²), CH₂SR², COR², CO₂R², CONR³R⁴, SO₂NR³R⁴, SO₃R², SO₂R⁵, SOR⁵, SR⁵, P(O)(OR³)(OR⁴), P(O)R⁵(OR³), P(O)R⁵R⁶, P(O)(OR²)NR³R⁴, P(O)(NR³R⁴)₂, P(O)-R⁵(NR³R⁴), Cl, Br, F, I, CF₃, or (CH₃)₀₋₆ aryl;

Y and Z independently are H or C₁₋₆ alkyl;

R², R³, and R⁴ independently are H, C₁₋₆ alkyl, C₃₋₅ alkenyl, or (CH₂)₀₋₆ aryl; and

35 R⁵ and R⁶ independently are C₁₋₆ alkyl, C₃₋₅ alkenyl, or (CH₂)₀₋₆ aryl; or a pharmaceutically acceptable salt thereof.

Compounds of Formula (I) are prepared by the synthetic pathways shown in Schemes I through IV. In Schemes I through IV, W, X, Y, and Z are as defined in Formula (I).

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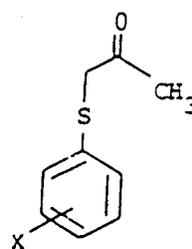
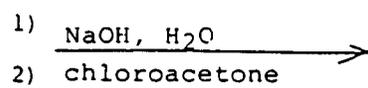
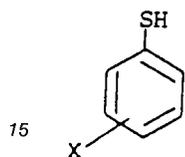
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SCHEME I

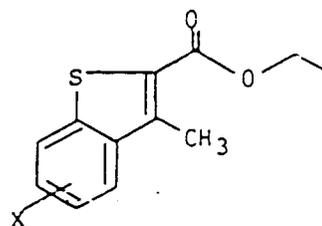
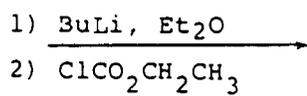
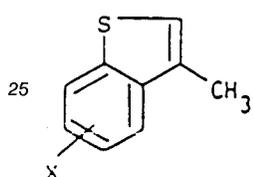
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Method A

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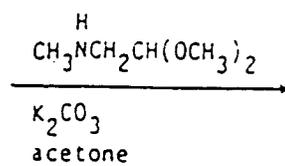
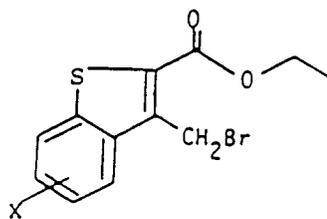
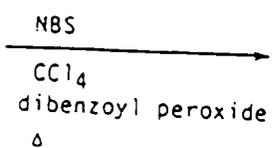


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(2)

(3)

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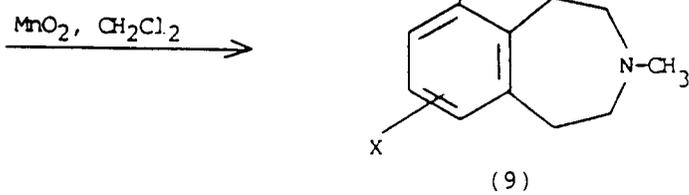
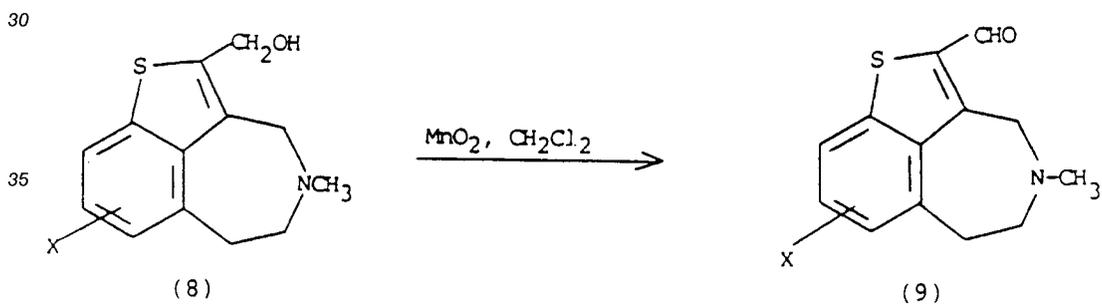
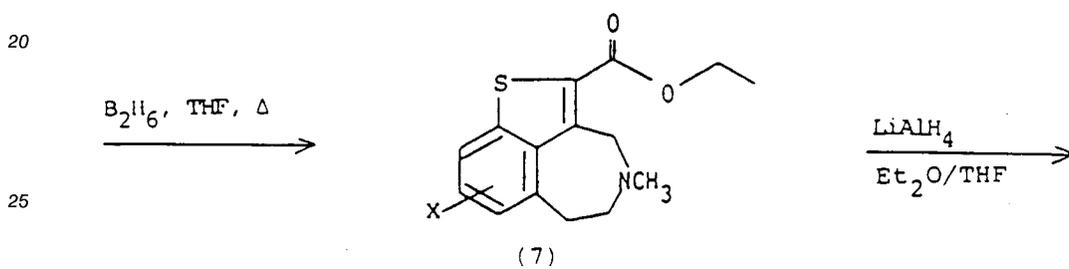
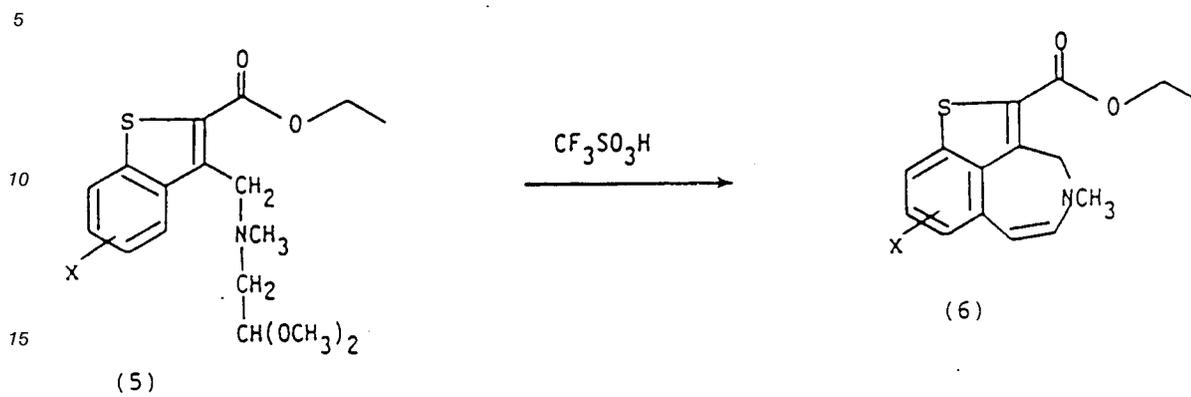
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SCHEME I (Continued)

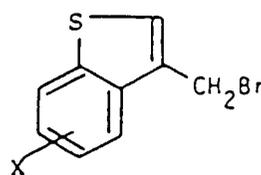
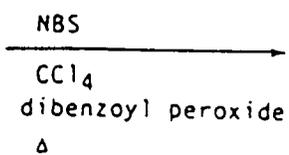
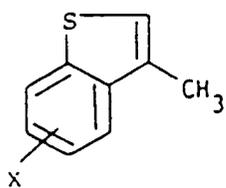


SCHEME I (Continued)

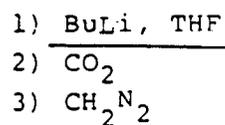
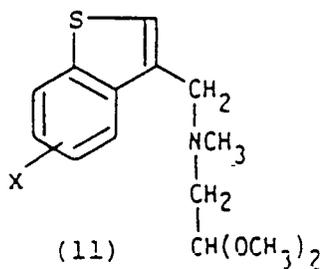
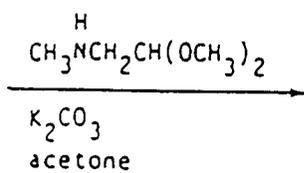
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Method B

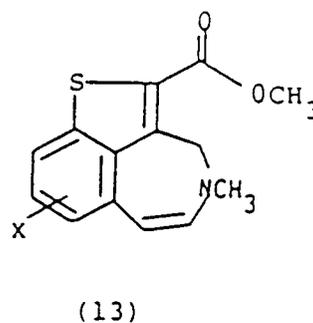
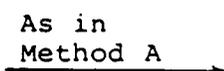
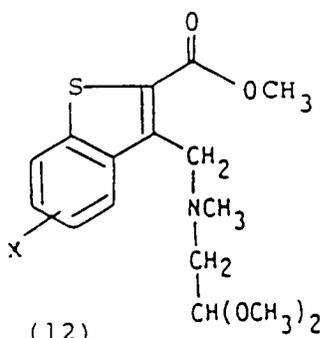
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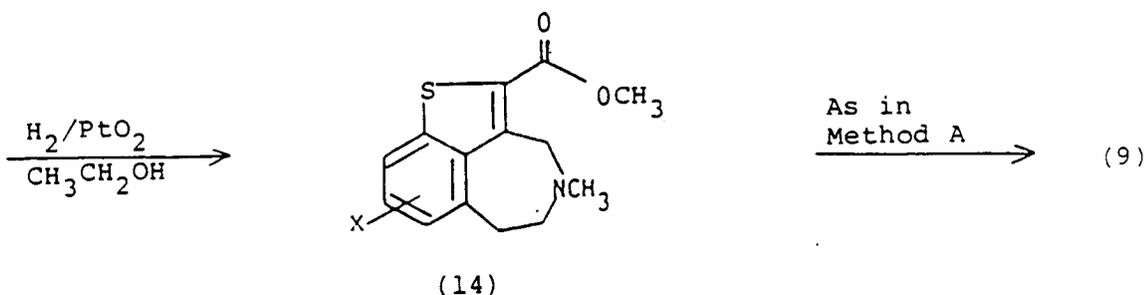
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SCHEME I (Continued)

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Scheme I, Method A, shows the synthesis of Formula (I) compounds in which the 2-position substituent is $\text{CO}_2\text{CH}_2\text{CH}_3$, CHO , and CH_2OH , which are α -adrenoceptor antagonists and which are also useful as intermediates in synthesis of other Formula (I) compounds. According to Scheme I, thiophenol or a substituted thiophenol is treated with a base such as sodium hydroxide in a suitable solvent such as water. The resulting sodium thiophenolates are heated at 0°C to 75°C , preferably 25°C , with a haloacetone, preferably chloroacetone to yield (phenylthio)propanones (1). Substituted benzo[b]thiophene formula (2) compounds are prepared by treating formula (1) compounds with a strong acid, preferably polyphosphoric acid (PPA), at from 0°C to 175°C , preferably 25°C to 130°C .

Formula (2) compounds are treated with a base, preferably butyllithium, in an inert solvent, preferably ethyl ether, at a suitable temperature, preferably 0°C , and then with an alkyl chloroformate, preferably ethyl chloroformate, at a suitable temperature, preferably 0°C , to produce formula (3) compounds.

Formula (3) compounds are treated with a halogenating agent, preferably N-bromosuccinimide (NBS), and an initiator, preferably dibenzoylperoxide, in an inert organic solvent, preferably carbon tetrachloride (CCl_4), preferably at reflux, to produce formula (4) compounds. Formula (5) compounds are prepared by dissolving formula (4) compounds in an organic solvent such as acetone and adding a suitable base, preferably potassium carbonate (K_2CO_3), and an N-(C_{1-6} alkyl)aminoacetaldehyde di(C_{1-4} alkyl) acetal, preferably methylaminoacetaldehyde dimethyl acetal.

Formula (5) compounds are treated with acid, preferably trifluoromethanesulfonic acid, to yield enamine compounds of formula (6). Formula (6) compounds are treated with a reducing agent, preferably diborane, in an inert organic solvent, such as tetrahydrofuran, at a suitable temperature, such as at reflux, or reduced catalytically with a suitable catalyst, preferably platinum oxide, in a suitable solvent, preferably ethanol, to give benzazepine compounds of formula (7).

Thereafter, formula (7) compounds are added to a suitable reducing agent, preferably lithium aluminum hydride (LAH), in an inert solvent, preferably ethyl ether, to yield formula (8) compounds. Formula (8) compounds are treated with a suitable oxidizing agent, preferably manganese dioxide, in an inert solvent, preferably dichloromethane, to give benzazepine-2-carboxaldehyde compounds of formula (9).

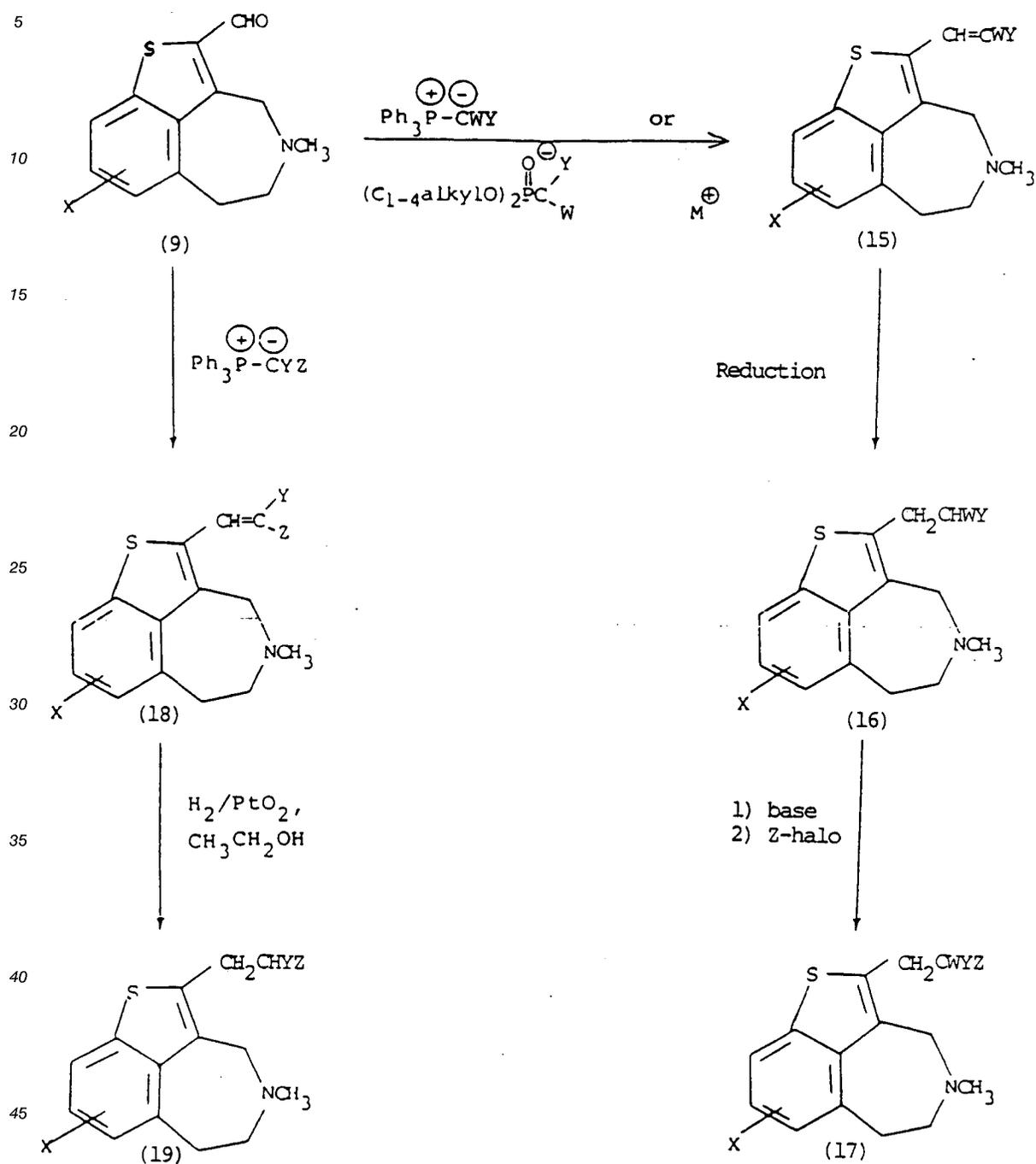
Scheme I, Method B, shows the synthesis of Formula (I) compounds in which the 2-position substituent is CO_2CH_3 . Formula (2) compounds are treated with a halogenating agent, preferably N-bromosuccinimide (NBS), and an initiator, preferably dibenzoylperoxide, in an inert organic solvent, preferably carbon tetrachloride (CCl_4), preferably at reflux, to produce formula (10) compounds.

Formula (11) compounds are prepared by dissolving formula (10) compounds in an organic solvent, such as acetone, and adding a suitable base, preferably potassium carbonate (K_2CO_3), and an N-(C_{1-6} alkyl)aminoacetaldehyde di(C_{1-4} alkyl) acetal, preferably methylaminoacetaldehyde dimethyl acetal.

Formula (11) compounds are treated with a strong base, preferably butyllithium, in an inert solvent, such as ethyl ether, at a suitable temperature, preferably -30°C , and then with carbon dioxide to produce carboxylic acids which are treated with an alkylating agent, such as diazomethane, in an inert solvent, such as ethyl ether, to give formula (12) compounds.

Formula (12) compounds are converted to formula (13), formula (14), formula (8) and formula (9) compounds as described for Method A.

SCHEME II



Scheme II shows synthesis of Formula (I) compounds in which the 2-position substituent is CH₂CWYZ. In Scheme II, X, W, Y and Z are as defined in Formula (I). According to Scheme II, formula (15) compounds are obtained from formula (9) compounds and a phosphonate or a phosphonium salt by treatment with a base, such as sodium hydride, in a suitable solvent, such as ethyl ether. The phosphonates or phosphonium salts are selected so that W and Y are the same as in the desired formula (17) compounds. The metal cation (M⁺) associated with the phosphonate is derived from the base used in this step on the synthesis. Suitable metal ions include lithium, sodium, and potassium.

Formula (15) compounds where W is CHO are prepared by reacting formula (9) compounds with a dialkyl phosphonoacetaldehyde dialkyl acetal, preferably diethyl phosphonoacetaldehyde diethyl acetal, followed by acid hydrolysis.

Formula (16) compounds where W is CO_2R^5 , COR^2 , SOR^5 , SO_2R^5 , SO_3R^{12} , $\text{SO}_2\text{NR}^3\text{R}^4$, $\text{P}(\text{O})\text{OR}^3(\text{OR}^4)$, $\text{P}(\text{O})\text{R}^5(\text{OR}^3)$, $\text{P}(\text{O})\text{R}^5\text{R}^6$, $\text{P}(\text{O})(\text{OR}^2)\text{NR}^3\text{R}^4$, $\text{P}(\text{O})(\text{NR}^3\text{R}^4)_2$, or $\text{P}(\text{O})\text{R}^5(\text{NR}^3\text{R}^4)$ are prepared by reduction of the corresponding formula (15) compounds with hydrogen and a suitable catalyst, preferably platinum oxide, in a suitable solvent, preferably ethanol.

5 Formula (15) compounds where W is CHO are reduced catalytically as the acetal followed by acid hydrolysis to produce formula (16) compounds wherein W is CHO.

Formula (16) compounds where W is NO_2 or CN are prepared by reduction of the corresponding formula (15) compounds with a metal hydride, preferably sodium borohydride, in a suitable solvent, preferably isopropanol.

10 Formula (16) compounds where W is CO_2H are prepared by hydrolyzing formula (16) compounds where W is CO_2R^5 with a strong acid, preferably hydrochloric acid in acetic acid. Formula (16) compounds where W is CONR^3R^4 are prepared from Formula (16) compounds where W is CO_2H by treatment with a known halogenating agent, such as thionyl chloride, followed by reaction with an amine HNR^3R^4 or by treatment of a formula (16) compound where W is CO_2R^5 with an amine HNR^3R^4 .

15 Formula (16) compounds may be converted to formula (17) compounds by treatment with a strong base, such as lithium diisopropylamide, in a suitable inert solvent, preferably tetrahydrofuran, to give an anion which is alkylated with an alkyl halide or an alkyl sulfonate.

Formula (18) compounds are prepared from formula (9) compounds by treatment with an alkyltriphenyl phosphonium salt, such as methyltriphenylphosphonium bromide, and a base, such as sodium hydride, in a suitable solvent, such as dimethylformamide and ethyl ether. The phosphonium salts are selected so that Y and Z are the same as in the desired formula (18) compounds. Formula (19) compounds are prepared from formula (18) compounds by reduction with hydrogen and a suitable catalyst, preferably platinum oxide, in a suitable solvent, such as ethanol.

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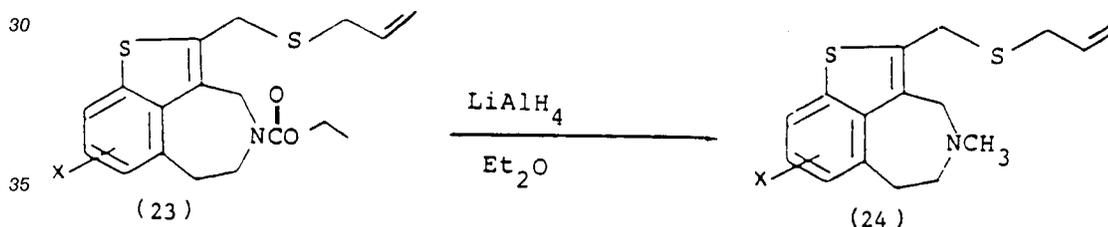
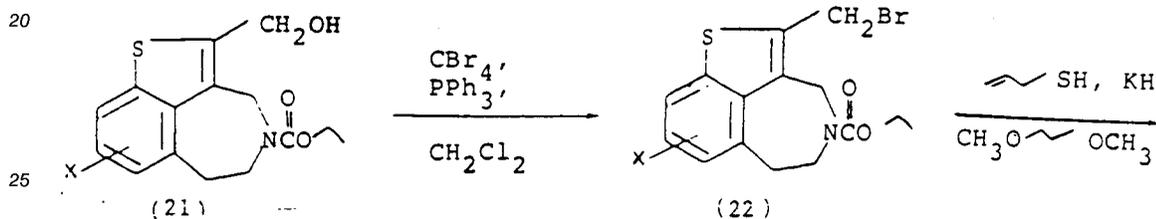
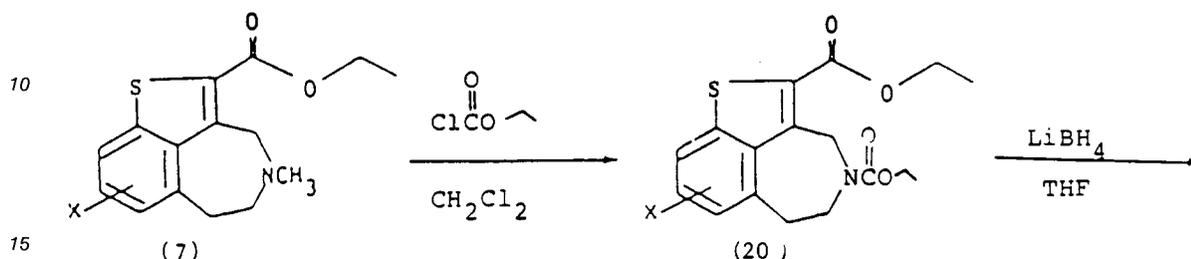
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SCHEME III

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40 Scheme III shows formation of Formula (I) compounds in which the 2-position substituent is W, CH₂CWYZ and CWYZ. In scheme III, X is as defined in Formula (I). According to Scheme III, formula (20) compounds are prepared from Scheme I, formula (7) compounds by treatment with a suitable haloformate, preferably ethyl chloroformate. Other haloformates, such as trichloroethyl chloroformate may also be employed. Formula (20) compounds are treated with a suitable reducing reagent, such as lithium borohydride, in a suitable solvent, preferably tetrahydrofuran, to give formula (21) compounds. Formula (22) compounds are prepared from formula (21) compounds by treatment with a suitable halogenating agent, such as carbon tetrabromide and triphenylphosphine, in a suitable solvent, preferably methylene chloride.

45 Formula (21) compounds also may be converted to chlorides or sulfonates by treatment with a suitable reagent, such as thionyl chloride or methanesulfonyl chloride, and a suitable base, such as triethylamine, in a suitable solvent, preferably methylene chloride. The halide or sulfonate group in formula (22) compounds may be displaced by a nucleophile, for example, cyanide ion, in a suitable solvent, such as acetonitrile, using a crown ether catalyst, such as 18-crown-6, to give Formula (I) compounds in which the 2-position substituent is CWYZ, where W is CN and Y and Z are each hydrogen atoms. This product may be elaborated further to produce Formula (I) compounds in which the 2-position substituent is CWYZ, where W is CN and Y and Z are each C₁₋₆ alkyl or Y is a hydrogen atom and Z is a C₁₋₆ alkyl group. These products may be formed by treatment of the above Formula (I) compounds with a strong base, such as lithium diisopropylamide, in a suitable inert solvent, preferably tetrahydrofuran, to give an anion which is alkylated with an alkyl halide or an alkyl sulfonate to produce the desired Formula (I) compounds.

Formula (I) compounds in which the 2-position substituent is $(\text{CH}_2)_2\text{CWYZ}$ are formed in a fashion similar to that described for the preparation of compounds in which the 2-position substituent is CWYZ . In this case, the starting alcohol is a Scheme II, formula (17) compound in which W is CH_2OH and Y and Z are each hydrogen atoms. These formula (17) compounds may be converted to chlorides or sulfonates by treatment with a suitable reagent, such as thionyl chloride or methanesulfonyl chloride, and a suitable base, such as triethylamine, in a suitable solvent, preferably methylene chloride. The halide or sulfonate group may be displaced by a nucleophile, for example, cyanide ion, in a suitable solvent, such as acetonitrile, using a crown ether catalyst, such as 18-crown-6, to give Formula (I) compounds in which the 2-position substituent is $(\text{CH}_2)_2\text{CWYZ}$ where W is CN and Y and Z are each hydrogen atoms. The desired Formula (I) compounds in which the 2-position substituent is $(\text{CH}_2)_2\text{CWYZ}$, where W is CN and Y and Z are each C_{1-6} alkyl or Y is a hydrogen atom and Z is a C_{1-6} alkyl group, may be prepared from the above Formula (I) compounds by treatment with a strong base, such as lithium diisopropylamide, in a suitable inert solvent, preferably tetrahydrofuran, to give an anion which is alkylated with an alkyl halide or an alkyl sulfonate.

Formula (I) compounds in which the 2-position substituent is C_{3-5} alkenyl, except where the double bond is in the 1-position, may be prepared from Scheme II, formula (17) compounds, where Y and Z are each hydrogen atoms or Y is a hydrogen atom and Z is a C_{1-6} alkyl group and W is CH_2OH . These formula (17) compounds may be treated with a halogenating agent, such as thionyl chloride, and a suitable base, such as triethylamine, to give the corresponding halides. These compounds may be treated with a strong base, such as lithium diisopropylamide, to give the desired Formula (I) compounds in which the 2-position substituent is C_{3-5} alkenyl, except where the double bond is in the 1-position.

Formula (23) compounds are prepared from formula (22) compounds by treatment with an alkyl mercaptan and a suitable base, preferably potassium hydride, in a suitable solvent, such as 1,2-dimethoxyethane.

Formula (24) compounds are prepared from formula (23) compounds by reduction with a suitable reagent, preferably lithium aluminum hydride, in a suitable solvent, such as ethyl ether.

Compounds of formula (22) also may be treated with a variety of known nucleophiles, examples being: nitrogen compounds, such as nitrite; carbon compounds, such as t-butyl lithioacetate; sulfur compounds, such as sodium phenylsulfinate; and phosphorus compounds, such as triethylphosphite; to give Formula (I) compounds.

Scheme I, formula (8) compounds also may be treated with halogenating agents, such as thionyl chloride, to give halo compounds similar to formula (22) compounds where the ethoxycarbonyl group is replaced by a methyl group. Halo compounds obtained from formula (8) compounds may be treated with a variety of nitrogen, carbon, sulfur and phosphorus nucleophiles to give Formula (I) compounds directly.

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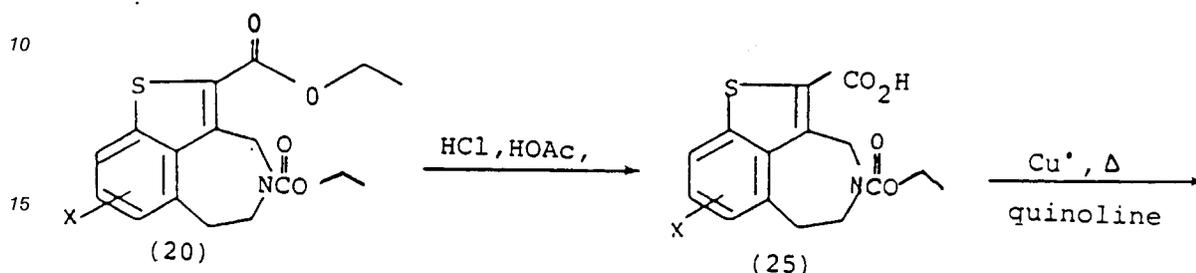
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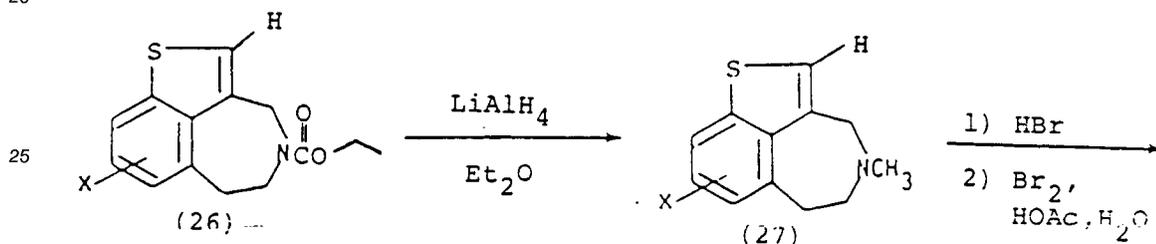
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SCHEME IV

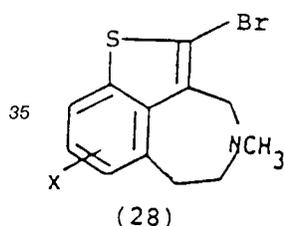
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Scheme IV illustrates preparation of Formula (I) compounds in which the 2-position substituent is hydrogen or halo. In Scheme IV, X is as defined in Formula (I). According to Scheme IV, formula (20) compounds are hydrolyzed to formula (25) compounds with strong acid, preferably hydrochloric acid in acetic acid. Formula (25) compounds are decarboxylated, preferably by treatment with copper powder and quinoline, at a temperature of 150° to 250° C, preferably 200° C, to give formula (26) compounds. Formula (26) compounds are reduced with a suitable reagent, preferably lithium aluminum hydride, in a suitable solvent, such as ethyl ether, to yield formula (27) compounds. Formula (27) compounds are converted to hydrobromides and treated with a suitable brominating agent, preferably bromine, in a suitable solvent, such as aqueous acetic acid, to yield formula (28) compounds.

Formula (I) compounds in which the 2-position substituent is chloro are prepared in a similar way by treating formula (27) compounds as their hydrochlorides with chlorine.

Formula (I) compounds in which the 2-position substituent is phenyl or a SR⁵ group are prepared from formula (27) compounds by treatment with a lithiating agent, such as butyl lithium, in a suitable solvent, such as tetrahydrofuran, to form the corresponding 2-lithio derivative. This intermediate is treated with a (R⁵)₂-disulfide species, wherein R⁵ is as defined in Formula (I) compounds, to form the 2-SR⁵ compounds. Alternately, the 2-lithio intermediate is treated with a tri-alkyltin halide, such as tributyltin chloride, followed by reaction with an aryl halide, such as iodobenzene, in the presence of a palladium catalyst, such as bis-(triphenylphosphine)palladium (II) chloride, to produce Formula (I) compounds wherein the 2-position

substituent is phenyl.

Schemes I through IV outline preparation of Formula (I) compounds in which R is methyl. Formula (I) compounds wherein R is other than methyl are formed by selecting the N-(C₁₋₆alkyl)aminoacetaldehyde di-(C₁₋₄alkyl)acetal used in preparing the formula (5) and (11) compounds of Scheme I so that the nitrogen is desirably substituted. Alternatively, Formula (I) compounds wherein R is other than methyl are prepared by reacting a Formula (I) compound wherein R is methyl with an alkyl haloformate, preferably trichloroethyl chloroformate, at approximately 50 °C to 100 °C to produce a trihaloalkyl carbamate. To this carbamate dissolved in a suitable organic solvent, such as tetrahydrofuran, is added an acid, preferably acetic acid, and a reducing agent, such as zinc dust, to yield a product in which R is hydrogen. This subsequently is reacted with a halo-R⁷ compound, wherein R⁷ is C₂₋₆alkyl or C₃₋₅alkenyl, to yield Formula (I) compounds wherein R is C₂₋₆alkyl or C₃₋₅alkenyl, respectively.

The substituted thiophenols and haloacetones used as starting materials in Scheme I are commercially available or can be synthesized from available materials by known methods. Additionally, the reactants used in Schemes I through IV are available or can be synthesized from available materials by known methods.

The pharmaceutically acceptable, nontoxic, acid addition salts having the utility of the free bases of Formula (I) are formed with inorganic or organic acids by methods well known in the art. Representative examples of suitable acids are maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

Because the compounds of Formula (I) are α -adrenoceptor antagonists they are useful in treating cardiovascular diseases in which changes in vascular resistance are desirable, including hypertension, pulmonary hypertension, congestive heart failure, myocardial ischemia, angina pectoris, and peripheral vascular disease. Formula (I) compounds also are useful in treating benign prostatic hypertrophy, diabetes, glaucoma, ocular hypertension, obesity, disorders of gastrointestinal motility, including colonic spasm, irritable bowel syndrome, and constipation, impotence, and central nervous system disorders such as depression and senile dementia. Additionally, the invented compounds are useful in treating diseases resulting from inappropriate platelet aggregation.

The α -adrenoceptor activity of certain compounds of the present invention was determined using the following *in vitro* systems.

Alpha₁ adrenoceptor antagonist activity was determined using the rabbit aorta. Male New Zealand White rabbits (2-4 Kg) were euthanized by cervical concussion. A 4 cm portion of the thoracic aorta was removed and placed in a dish of cold (10 °C) Krebs-Hensleit solution. The tissue was cleaned of fat and connective tissue and cut into segments of approximately 3 mm in length. These segments were suspended in 10 ml tissue baths via hangers constructed of 0.25 mm tungsten wire. One hanger was fixed to a support in the bath and the other was attached via silk thread to a force-displacement transducer.

Tissue segments were equilibrated for 2 hours prior to drug testing, during which time basal tension was maintained at 2 gm. Tissues were washed at 30 minute intervals during this equilibration period. The Krebs-Hensleit solution contained cocaine (6 μ M) to block neuronal uptake and propranolol (1 μ M) to block beta adrenoceptors. Tissues were usually challenged once with norepinephrine (0.1 μ M) during the equilibration period to check for viability.

A cumulative concentration-response curve to norepinephrine was obtained in each aortic segment. Following washout of norepinephrine, the α adrenoceptor antagonist to be tested was added to the bath. After the tissue had been in contact with the antagonist for 30-60 minutes, the norepinephrine concentration response-curve was repeated in the presence of antagonist. The tissue was then washed again, and a tenfold higher concentration of antagonist added. Following equilibration (30-60 minutes), a third norepinephrine concentration-response curve was determined in the presence of the antagonist.

The receptor dissociation constant (K_B) for the antagonist was determined using the relationship

$$K_B = \frac{\text{Antagonist Concentration}}{\text{Dose Ratio} - 1}$$

(Furchgott, R. F; *Handbook of Experimental Pharmacology*, eds. Eichler, et al., pp. 283-335 (Springer 1972)-). The K_B value obtained at each antagonist concentration was averaged to obtain a mean K_B for each experiment.

Alpha₂ adrenoceptor antagonist activity of the compounds was determined using the isolated, superfused guinea pig left atrium. Briefly, the heart is removed from a pentobarbital-anesthetized male guinea

5 pig. The left atrium is separated, dissected free of extraneous tissue and mounted in a 2 ml superfusion chamber. The tissue is paced at 30 pulse/minute and the sympathetic nerves excited at 6 minute intervals by field stimulation. The response to nerve stimulation is measured as the difference in contractile force between the basal contraction and peak contraction following a nerve stimulation. A concentration-response curve for B-HT 920 (a known α_2 agonist) is prepared by administering increasing concentrations of B-HT 920 following each successive stimulation. The tissue then is superfused for thirty minutes with the α -adrenoceptor antagonist to be tested and the B-HT 920 concentration-effect curve is repeated in the presence of antagonist. Data are reported as K_B , defined above. Additional details of this test system are found in Hieble, J. P. and R. G. Pendleton, *Arch. Pharmacol.*, 309:217-224 (1979).

10 α_3 adrenoceptor antagonist receptor activity was determined using the dog saphenous vein (DSV) as the test system. This test system has been shown a suitable preparation in which to characterize postsynaptic α_2 (α_3) adrenoceptors, Sullivan, A. T. and G. M. Drew, *Arch. Pharmacol.*, 314:249-58 (1980). This test system is prepared by removing the lateral saphenous vein from an anesthetized dog and cutting the vein into segments of 4 mm in length. Segments are mounted as described for the isolated rabbit aorta.

15 The α_3 adrenoceptor antagonist activity of the compounds of interest is determined by measuring shifts in the dose-response curve of a specific agonist induced by the tested compounds. The α_2 , α_3 agonist, B-HT 920, was used in testing the compounds listed in Table I.

20 Representative Formula (I) compounds which were tested using the above described *in vitro* test systems are listed in Table 1. Each of the compounds tested was found to have activity at one or more of the α adrenoceptor subtypes.

Table 1

25 ethyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate;
7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol;
7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde;
methyl-7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate;
7-chloro-3,4,5,6-tetrahydro-4-methyl-2-[(2-propenyloxy)methyl]thieno[4,3,2-ef][3]benzazepine;
7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine;
30 7-chloro-3,4,5,6-tetrahydro-2,4-dimethylthieno[4,3,2-ef][3]benzazepine;
7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-ethan-2-ol;
7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-ethan-2-one;
7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxamide;
N,N-dimethyl-7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]-2-benzazepine-carboxamide;
35 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-(1-methylethyl)thieno[4,3,2-ef][3]benzazepine;
7-chloro-2-ethyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine;
7-chloro-2-propyl-3,4,5,6-tetrahydro-4-methyl-thien o[4,3,2-ef][3]benzazepine; or
2,7-dichloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine.

40 Novel pharmaceutical compositions are obtained when the compounds are incorporated with pharmaceutical carriers into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutical carriers can be employed. Solid carriers include, starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid, or an aqueous or nonaqueous liquid suspension or solution.

45 The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating and compressing, when necessary, for tablet forms, or mixing, filling, and dissolving the ingredients, as appropriate, to give the desired oral or parenteral products.

50 Doses of the present compounds in pharmaceutical dosage units will be an efficacious, nontoxic quantity selected from the range of 0.01-100 mg/kg of active compound, preferably 0.1-50 mg/kg. The selected dose is administered to a human patient in need of treatment from 1-6 times daily, orally, rectally, topically, by inhalation, or injection, or continuously by infusion. Oral administration, however, is preferred because it is more convenient for the patient.

55 The following examples are illustrative of preparation of Formula (I) compounds. The examples are not intended to limit the scope of the invention as defined hereinabove and as claimed below.

EXAMPLE 1

Method A -- Ethyl 7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate5 i) 1-[(4-Chlorophenyl)thio]-2-propanone

Chloroacetone (32.3 g 0.347 mol) was added to a mixture of 4-chlorothiophenol (50 g, 0.347 mol) and sodium hydroxide (14 g, 0.347 mol) in water (400 ml) and the mixture was stirred at 25 °C for 1 hour. The mixture was extracted with ethyl ether and the organic phase was washed with water, dried with magnesium sulfate and concentrated to give 68 g (98%) of 1-[(4-chlorophenyl)thio]-2 propanone.

10 ii) 5-Chloro-3-methylbenzo[b]thiophene

1-[(4-Chlorophenyl)thio]-2-propanone (50 g, 0.25 mol) was added to polyphosphoric acid (300 g) and the mixture was stirred as the temperature was gradually raised to 120 °C as an exotherm started. The mixture was stirred at 130 °C for 1 hour, diluted with water, extracted with ethyl ether and the organic phase was dried and concentrated. The residue was stirred in methanol (200 ml), filtered and the filtrate concentrated to give 17.5 g (40%) of 5-chloro-3-methylbenzo[b]thiophene: bp 120 °C (0.6 mm).

20 iii) Ethyl 5-chloro-3-methylbenzo[b]thiophene-2-carboxylate

Butyllithium in hexane (2.6 M, 2.3 ml) was added to a solution of 5-chloro-3-methylbenzo[b]thiophene (1.0 g, 6 mmol) in ethyl ether (20 ml) stirred at 0 °C under argon. The mixture was stirred for 30 minutes and transferred slowly under argon pressure to a stirred solution of ethyl chloroformate (0.63 g, 6 mmol) in ethyl ether (20 ml). The mixture was stirred at 0 °C for 30 minutes and at 25 °C for 1.5 hours. The mixture was treated with water and the organic phase was dried, concentrated and triturated with hexane to give 1.0 g (67%) of ethyl 5-chloro-3-methylbenzo[b]thiophene-2-carboxylate: mp 92.5-94 °C.

30 iv) Ethyl 3-Bromomethyl-5-chlorobenzo[b]thiophene-2-carboxylate

A mixture of ethyl 5-chloro-3-methylbenzo[b]thiophene-2-carboxylate (9.0 g, 0.035 mol), N-bromosuccinimide (6.53 g, 0.037 mol) and benzoyl peroxide (130 mg) in carbon tetrachloride (150 ml) was refluxed and illuminated with a sunlamp for 2 hours. The resulting suspension was cooled, filtered and the filter cake was triturated with methanol to give 9.9 g (85%) of the methanol-insoluble ethyl 3-bromomethyl-5-chlorobenzo [b]thiophene 2-carboxylate: mp 148-150 °C.

35 v) Ethyl 5-Chloro-3-[N-(2,2-dimethoxyethyl)-N-methyl(aminomethyl)]benzo[b]thiophene-2-carboxylate

A mixture of ethyl 3-bromomethyl-5-chlorobenzo[b]thiophene-2-carboxylate (11.0 g. 0.033 mol), methylaminoacetaldehyde dimethyl acetal (4.76 g, 0.04 mol) and potassium carbonate (11.4 g, 0.8 mol) in dry acetone (200 ml) was stirred for 48 hours, filtered and the filtrate concentrated to give 11.8 g (96%) of ethyl 7-chloro-3-[N-(2,2-dimethoxyethyl)-N-methyl-(aminomethyl)]benzo[b]thiophene-2-carboxylate.

45 vi) Ethyl 7-Chloro-3,4-dihydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate

Ethyl 5-chloro-3-[N-(2,2-dimethoxyethyl)-N-methyl(aminomethyl)]benzo[b]thiophene-2-carboxylate (3.0 g, 8.1 mmol) was added in portions to trifluoromethanesulfonic acid (10 ml) stirred at 0 °C under argon. The mixture was stirred for 25 °C for 45 minutes and diluted with water. The mixture was basified with aqueous sodium hydroxide and extracted with ethyl ether to give ethyl 7-chloro-3,4-dihydro-4-methylthieno[4,3,2-ef]-[3]benzazepine-2-carboxylate.

50 vii) Ethyl 7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate

Diborane in tetrahydrofuran (1 M, 40 ml) was added to a solution of ethyl 7-chloro-3,4-dihydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate (2.8 g) in tetrahydrofuran (30 ml) stirred at 0 °C. The mixture was refluxed for 3 hours and stirred at 25 °C for 16 hours, cooled, treated with methanol (50 ml), refluxed for 18 hours and concentrated. The residue was triturated with ethyl ether-hexane (3:1) to give 1.6 g (64%) of ethyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate: mp 138-

140 °C. The free base was treated with hydrogen chloride to give ethyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate hydrochloride: mp 240 °C.

Method B -- Methyl 7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate

5

i) 3-Bromomethyl-5-chlorobenzo[b]thiophene

Using the general procedure of Example 1, Method A, (iv), replacing ethyl 5-chloro-3-methylbenzo[b]thiophene-2-carboxylate with 5-chloro-3-methylbenzo[b]thiophene gave 2.78 g (57%) of 3-bromomethyl-5-chlorobenzo[b]thiophene: mp 126-128 °C.

10

ii) 5-Chloro-3-[N-(2,2-dimethoxyethyl)-N-methyl(aminomethyl)]benzo[b]thiophene

Using the general procedure of Example 1, Method A, (v), replacing ethyl 3-bromomethyl-5-chlorobenzo[b]thiophene-2-carboxylate with 3-bromomethyl-5-chlorobenzo[b]thiophene gave 2.1 g (95%) of 5-chloro-3-[N-(2,2-dimethoxyethyl)-N-methyl(aminomethyl)]benzo[b]thiophene.

15

iii) 5-Chloro-3-[N-(2,2-dimethoxyethyl)-N-methyl(aminomethyl)]benzo[b]thiophene-2-carboxylic Acid

Butyllithium in tetrahydrofuran (2.6 M, 0.04 mol) was added slowly to a solution of 5-chloro-3-[N-(2,2-dimethoxyethyl)-N-methyl(aminomethyl)]benzo[b]thiophene (10 g, 0.033 mol) in freshly distilled tetrahydrofuran (100 ml) stirred at -30 °C under argon. The mixture was stirred for 30 minutes, treated with dry carbon dioxide for 5 minutes and allowed to warm to 25 °C. The mixture was treated with methanol, poured into ice water and extracted with ethyl ether. The aqueous phase was adjusted to pH 7.5 and extracted with methylene chloride. The organic phase was washed with water, dried with magnesium sulfate and concentrated to give 6.0 g (54%) of 5-chloro-3-[N-(2,2-dimethoxyethyl)-N-methyl(aminomethyl)]benzo[b]thiophene-2-carboxylic acid.

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iv) Methyl 5-Chloro-3-[N-(2,2-dimethoxyethyl)-N-methyl(aminomethyl)]benzo[b]thiophene-2-carboxylate

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A suspension of 5-chloro-3-[N-(2,2-dimethoxyethyl)-N-methyl(aminomethyl)]benzo[b]thiophene-2-carboxylic acid (5.0 g, 14.5 mmol) in methylene chloride-tetrahydrofuran was stirred at 0 °C and treated with excess diazomethane in ethyl ether. The mixture was stirred for 2 hours at 0 °C, treated with a stream of argon and concentrated to give 5.0 g (96%) of methyl 5-chloro-3-[N-(2,2-dimethoxyethyl)-N-methyl(aminomethyl)]benzo[b]thiophene-2-carboxylate.

35

v) Methyl 7-Chloro-3,4-dihydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate

Using the general procedure of Example 1, Method A, (vi), replacing ethyl 5-chloro-3-[N-(2,2-dimethoxyethyl)-N-methyl(aminomethyl)]benzo[b]thiophene-2-carboxylate with methyl 5-chloro-3-[N-(2,2-dimethoxyethyl)-N-methyl(aminomethyl)]benzo[b]thiophene-2-carboxylate gave methyl 7-chloro 3,4-dihydro-4-methylthieno[4,3,2-ef][3]benzazepine 2 carboxylate.

40

vi) Methyl 7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate

45

A solution of methyl 7-chloro-3,4-dihydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate in ethanol (30 ml) containing platinum oxide (0.3 g) was shaken under hydrogen (30 psi) for 2 hours. The mixture was filtered, concentrated and treated with ethereal hydrogen chloride to give methyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate hydrochloride: mp 215-216 °C.

50

EXAMPLE 2

7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol

A solution of methyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate (4.0 g, 13.5 mmol), prepared as in Example 1, in ethyl ether (48 ml) was treated with lithium aluminum hydride (0.53 g, 14 mmol). The mixture was stirred for 1.5 hours, cooled and treated carefully with water (2.0 ml), 10% sodium hydroxide (1.0 ml) and water (2.0 ml). The resulting mixture was filtered and the solvent

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evaporated to give 2.1 g (57%) of 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol: mp 184-185 °C.

EXAMPLE 3

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7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde

A solution of 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol, prepared as in Example 2, (1.6 g, 6 mmol) in dichloromethane (150 ml) was stirred under argon with activated manganese dioxide (8.3 g) for 2 hours. The mixture was filtered through an acid washed silicon dioxide filtration agent (Celite®) and the filtrate was dried with magnesium sulfate and concentrated to give a 63% yield of 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde.

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EXAMPLE 4

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7-Chloro-3,4,5,6-tetrahydro-4-methylthieno [4,3,2-ef][3]benzazepine-2-carboxylic Acid

A mixture of ethyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate, prepared as in Example 1, (30 g), 6N hydrochloric acid (300 ml) and acetic acid (300 ml) was heated to reflux for 3 hours, cooled and filtered to give 15 g of 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylic acid hydrochloride. The filtrate was concentrated in vacuo and filtered to give an additional 13 g of product.

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EXAMPLE 5

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t-Butyl 7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate

A mixture of ethyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate, prepared as in Example 1, 5A molecular sieves, t-butanol and dry toluene is treated with potassium t-butoxide and stirred at 80 °C to give t-butyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate.

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EXAMPLE 6

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7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carbonyl Chloride and 2-Propenyl 7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate

A mixture of 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylic acid hydrochloride, prepared as in Example 4, (28 g) and thionyl chloride (100 ml) in toluene (50 ml) was heated to reflux for 5 hours, cooled and concentrated in vacuo. The residue was treated with toluene, concentrated in vacuo and the residue was stirred with ethyl ether and filtered to give 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carbonyl chloride hydrochloride: mp 27 °C.

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A suspension of 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carbonyl chloride hydrochloride in tetrahydrofuran is stirred and treated with allyl alcohol and triethylamine to give 2-propenyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate hydrochloride.

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EXAMPLE 7

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7-Chloro-3,4,5,6-tetrahydro-N,N,4-trimethylthieno[4,3,2-ef][3]benzazepine-2-carboxamide

Dimethylamine was bubbled through a mixture of 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carbonyl chloride hydrochloride, prepared as in Example 6, (0.5 g) in tetrahydrofuran (30 ml) stirred at -20 °C for 5 minutes. The mixture was stirred and allowed to warm to 25 °C for 2 hours, concentrated in vacuo, diluted with water and extracted with methylene chloride. The organic phase was dried with magnesium sulfate and concentrated in vacuo to give an oil which was chromatographed on silica gel eluted with methanol-methylene chloride (1:10) to give 125 mg of 7-chloro-N,N-dimethyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxamide: mp 103-105 °C.

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EXAMPLE 87-Chloro-3,4,5,6-tetrahydro- α,α ,4-trimethylthieno[4,3,2-ef][3]benzazepine-2-acetonitrile

5 A solution of 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol (0.01 mole), prepared as in Example 2, in thionyl chloride (30 ml) was heated to reflux under argon, cooled and concentrated to give 7-chloro-2-chloromethyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine hydrochloride.

10 A mixture of 7-chloro-2-chloromethyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine (5.0 mmol), potassium cyanide (10 mmol) and 18-crown-6 (0.1 mmol) in dry acetonitrile (25 ml) is stirred vigorously at room temperature. The reaction mixture is filtered and concentrated to one-third its volume, basified with 5% sodium bicarbonate and extracted with methylene chloride. The organic phase is dried and concentrated to give 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-acetonitrile.

15 A solution of 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-acetonitrile (3.0 mmol) in anhydrous tetrahydrofuran (25 ml) at -78° is treated with lithium diisopropylamide (6.0 mmol). The mixture is stirred and treated with a solution of methyl iodide (6.0 mmol) in dry tetrahydrofuran (5 ml) added dropwise. The reaction mixture is stirred, quenched with water and concentrated. The resulting residue is extracted with ether and the organic phase is dried and concentrated to give 7-chloro-3,4,5,6-tetrahydro- α,α ,4-trimethylthieno[4,3,2-ef][3]benzazepine-2-acetonitrile.

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EXAMPLE 97-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine 2-carboxaldehyde Oxime and 7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carbonitrile

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7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde, prepared as in Example 3, is added to a solution of hydroxylamine hydrochloride to give 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde oxime hydrochloride.

30 A mixture of 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde oxime hydrochloride and triethylamine in methylene chloride is stirred and cooled to -78°C and treated with a solution of trifluoromethanesulfonic anhydride in methylene chloride to give 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carbonitrile.

EXAMPLE 10

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2-Acetyl-7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine

Methylmagnesium bromide in tetrahydrofuran (3M, 15 ml, 45 mmol) was added to a solution of ethyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate, prepared as in Example 1, Method A, (3.09 g, 10 mmol) in ethyl ether (100 ml) stirred under argon. The mixture was stirred for 1 hour, treated with saturated aqueous ammonium chloride and extracted with ethyl ether. The organic phase was dried with magnesium sulfate and concentrated in vacuo to give a residue which was chromatographed on silica gel eluted with methanol-methylene chloride (1:10) to give 2-acetyl-7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine: mp $78-80^{\circ}\text{C}$.

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EXAMPLE 117-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine

50 A solution of ethyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate, prepared as in Example 1, (5.0 g, 16 mmol) in 1,2-dichloroethane (80 ml) was treated with ethyl chloroformate (8.3 g, 80 mmol) and heated to reflux for 7 hours. The mixture was concentrated in vacuo and the residue recrystallized from ethanol to give 3 g of ethyl 7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine-2-carboxylate.

55 Ethyl 7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine-2-carboxylate (3.0 g) in acetic acid (80 ml) and 6N hydrochloric acid (40 ml) was heated to reflux for 10 hours, cooled and filtered to give 1.8 g of 7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine-2-carboxylic acid.

A mixture of 7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine-2-carboxylic acid (0.6 g) and activated copper powder (1.0 g) in quinoline (10 ml) was heated to 200 °C for 30 minutes to give 7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine.

5 A solution of 7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine (0.5 g, 1.7 mmol) in ethyl ether (25 ml) was treated with lithium aluminum hydride (78 mg, 2 mmol) and stirred for 1.5 hours. The mixture was treated with water (2 drops), 10% aqueous sodium hydroxide (4 drops) and water (8 drops), filtered and the filtrate was concentrated in vacuo. The residue was treated with ethereal hydrogen bromide to give 0.34 g (xx%) of 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine hydrobromide: mp 248 °C.

10 Alternatively, 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylic acid hydrochloride, prepared as in Example 4, (3.0 g) was heated to 285 °C for 5 minutes, cooled and the residue partitioned between ethyl ether and water. The organic phase was dried with magnesium sulfate and concentrated in vacuo to give 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine.

15 EXAMPLE 12

7-Chloro-3,4,5,6 tetrahydro-2,4-dimethylthieno[4,3,2-ef][3]benzazepine

20 A solution of 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol hydrochloride, prepared as in Example 2, (0.2 g) in ethanol (30 ml) was treated with concentrated hydrochloric acid (5 drops) and platinum oxide (160 mg) and was shaken under hydrogen for 6 hours. The mixture was filtered, concentrated in vacuo, basified and extracted with ethyl ether. The organic phase was concentrated in vacuo and the residue was chromatographed on a preparative silica gel plate eluted with methanol-methylene chloride (1:10) to give an oil. The oil was dissolved in ethyl ether and treated with ethereal
25 hydrogen chloride to give 7-chloro-3,4,5,6-tetrahydro-2,4-dimethylthieno[4,3,2-ef][3]benzazepine hydrochloride: mp 252 °C.

EXAMPLE 13

30 7-Chloro-2-ethyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine

Using the general procedure of Example 12, replacing 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol hydrochloride with 7-chloro-2-ethenyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine hydrochloride gave 7-chloro-2-ethyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]-
35 benzazepine hydrochloride: mp 195 °C.

EXAMPLE 14

40 7-Chloro 3,4,5,6 tetrahydro-4-methyl-2-(2-methylpropyl)thieno[4,3,2-ef][3]benzazepine

A solution of butyllithium in hexane is added to a suspension of isopropyltriphenylphosphonium iodide in freshly distilled tetrahydrofuran stirred under argon at -15 °C. The mixture is stirred at -10 °C to -15 °C for 20 minutes and treated with a solution of 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde, prepared as in Example 3, in tetrahydrofuran added dropwise to give 7-chloro-3,4,5,6-
45 tetrahydro-4-methyl-2-(2-methyl-1-propenyl)thieno[4,3,2-ef][3]benzazepine.

Using the procedure of Example 12, replacing 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol hydrochloride with 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-(2-methyl-1-propenyl)-
thieno[4,3,2-ef][3]benzazepine hydrochloride gives 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-(2-methylpropyl)-
thieno[4,3,2-ef][3]benzazepine hydrochloride.

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EXAMPLE 15

Ethyl 7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-propanoate

55 A 50% dispersion of sodium hydride in mineral oil (58 mg, 1.2 mmol) was added to a stirred solution of triethyl phosphonoacetate (268 mg, 1.2 mmol) in ethyl ether (30 ml) and stirred for 15 minutes. The mixture was treated with a solution of 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde, prepared as in Example 3, (300 mg, 1.4 mmol) in ethyl ether (30 ml), stirred at 25 °C for 16 hours,

quenched with water and extracted with ethyl ether. The organic phase was washed, dried and concentrated and the residue was treated with ethereal hydrogen chloride to give 230 mg (40%) of ethyl (E)-3-(7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin-2-yl)-2-propenoate hydrochloride: mp 234-236 ° C.

Using the general procedure of Example 12, replacing 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol hydrochloride with ethyl (E)-3-(7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin-2-yl)-2-propenoate hydrochloride gives ethyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-propanoate hydrochloride.

EXAMPLE 16

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7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-propanol

Using the general procedure of Example 2, replacing ethyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate with ethyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-propanoate, prepared as in Example 15, gives 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-propanol.

EXAMPLE 17

20 7-Chloro-2-(3-chloropropyl)-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine and 7-Chloro-3,4,5,6-tetrahydro-4-methyl-2-(2-propenyl)thieno[4,3,2-ef][3]benzazepine

7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-propanol hydrochloride, prepared as in Example 16, is treated with thionyl chloride and triethylamine in chloroform to give 7-chloro-2-(3-chloropropyl)-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine hydrochloride.

7-Chloro-2-(3-chloropropyl)-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine is converted to the free base and treated with lithium diisopropylamide in tetrahydrofuran to give 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-(2-propenyl)thieno[4,3,2-ef][3]benzazepine.

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EXAMPLE 18

7-Chloro-3,4,5,6-tetrahydro- α,α ,4-trimethylthieno[4,3,2-ef][3]benzazepine-2-butanenitrile

Using the general procedure of Example 8, replacing 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol with 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-propanol, prepared as in Example 16, gives 7-chloro-3,4,5,6-tetrahydro- α,α ,4-trimethylthieno[4,3,2-ef][3]benzazepine-2-butanenitrile.

EXAMPLE 19

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7-Chloro-3,4,5,6-tetrahydro-4-methyl-2-[(2-propenyloxy)methyl]thieno[4,3,2-ef][3]benzazepine

A solution of 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol, prepared as in Example 2, (0.2 g, 0.75 mmol) in dimethylformamide (20 ml) was treated with a 50% dispersion of sodium hydride (37 mg, 0.78 mmol), stirred for 15 minutes, treated with allyl iodide (126 mg, 0.75 mmol) and stirred for 18 hours. The usual workup gave an oil which was dissolved in ethyl ether and treated with hydrogen chloride to give 0.15 g (58%) of 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-[(2-propenyloxy)methyl]thieno[4,3,2-ef][3]benzazepine hydrochloride: mp 140-142 ° C.

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EXAMPLE 20

7-Chloro-3,4,5,6-tetrahydro-4-methyl-2-[(propyloxy)methyl]thieno[4,3,2-ef][3]benzazepine

Using the general procedure of Example 12, replacing 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol hydrochloride with 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-[(2-propenyloxy)methyl]thieno[4,3,2-ef][3]benzazepine hydrochloride, prepared as in Example 19, gives 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-[(propyloxy)methyl]thieno[4,3,2-ef][3]benzazepine hydrochloride.

EXAMPLE 217-Chloro-3,4,5,6-tetrahydro-4-methyl-2-[(3-methyl-2-butenyloxy)methyl]thieno[4,3,2-ef][3]benzazepine

5 Using the procedure of Example 19, replacing allyl iodide with 3-methyl-2-butenyl bromide, gives 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-[(3-methyl-2-butenyloxy)methyl]thieno[4,3,2-ef][3]benzazepine hydrochloride

EXAMPLE 22

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7-Chloro-3,4,5,6-tetrahydro-4-methyl-2-[(2-propenylthio)methyl]thieno[4,3,2-ef][3]benzazepine

15 A solution of ethyl 7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine-2-carboxylate, prepared as in Example 11, in tetrahydrofuran is stirred under argon and treated with 2 M lithium borohydride in tetrahydrofuran followed by trimethyl borate to give 7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine-2-methanol.

20 A solution of 7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine-2-methanol and carbon tetrabromide in methylene chloride is stirred at 0 °C and treated with triphenylphosphine. The mixture is stirred for 20 minutes at 0 °C, concentrated and the residue chromatographed on silica gel eluted with chloroform to give 2-bromomethyl-7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine.

25 Using the general procedure of Example 19, replacing 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol with allyl mercaptan and allyl iodide with 2-bromomethyl-7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine gives 7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydro-2-[(2-propenylthio)methyl]thieno[4,3,2-ef][3]benzazepine.

30 Using the general procedure of Example 11, replacing 7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine with 7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydro-2-[(2-propenylthio)methyl]thieno[4,3,2-ef][3]benzazepine gives 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-[(2-propenylthio)methyl]thieno[4,3,2-ef][3]benzazepine.

EXAMPLE 232-Bromo-7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine

35 A solution of 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine, prepared as in Example 11, in acetic acid is treated with hydrogen bromide and then with bromine to give 2-bromo-7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine hydrobromide.

EXAMPLE 24

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7-Chloro-3,4,5,6-tetrahydro-4-methyl-2-(trifluoromethyl)thieno[4,3,2-ef][3]benzazepine

45 A solution of 7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine, prepared as in Example 11, in acetic acid is treated with a solution of bromine in acetic acid to give 2-bromo-7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine.

50 A mixture of 2-bromo-7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine, trifluoromethyl iodide and activated copper in dimethylformamide is heated in a stainless steel pressure vessel to 150 °C for 48-72 hours. The mixture is cooled, diluted with water and ethyl acetate, filtered through an acid washed silicon dioxide filtration agent (Celite®) and the organic phase is washed with water and brine, dried with sodium sulfate and concentrated. The residue is chromatographed on silica gel to give 7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydro-2-(trifluoromethyl)thieno[4,3,2-ef][3]benzazepine.

55 Using the general procedure of Example 11, 7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine is replaced with 7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydro-2-(trifluoromethyl)thieno[4,3,2-ef][3]benzazepine to give 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-(trifluoromethyl)thieno[4,3,2-ef][3]benzazepine.

EXAMPLE 257-Chloro-3,4,5,6-tetrahydro-4-methyl-2-nitrothieno[4,3,2-ef][3]benzazepine

5 Using the general procedure of Example 23, replacing bromine with nitric acid gives 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-nitrothieno[4,3,2-ef][3]benzazepine.

EXAMPLE 2610 Ethyl 7-Chloro-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine-2-carboxylate

A mixture of ethyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate, prepared as in Example 1, (4.5 g, 14.5 mmol), trichloroethyl chloroformate (12.7 g, 58 mmol) and potassium carbonate (1.0 g) in toluene (100 ml) was heated to reflux for 72 hours, cooled and filtered. The filtrate was concentrated in vacuo, let stand and filtered to give 2.1 g of ethyl 7-chloro-3,4,5,6-tetrahydro-2-(trichloroethoxycarbonyl)thieno[4,3,2-ef][3]benzazepine-2-carboxylate.

A mixture of ethyl 7-chloro-3,4,5,6-tetrahydro-2-(trichloroethoxycarbonyl)thieno[4,3,2-ef][3]benzazepine-2-carboxylate (2.1 g) and zinc powder (4.5 g) in acetic acid was stirred for 72 hours, filtered and the filtrate was diluted with water, basified with 50% aqueous sodium hydroxide and extracted with ethyl ether. The organic phase was dried with magnesium sulfate and concentrated in vacuo to give 0.84 g of ethyl 7-chloro-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine-2-carboxylate.

EXAMPLE 2725 7-Chloro-4-ethyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine-2-methanol

A solution of ethyl 7-chloro-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine-2-carboxylate, prepared as in Example 26, and triethylamine in dry tetrahydrofuran is stirred and treated with acetyl chloride to give ethyl 4-acetyl-7-chloro-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine-2-carboxylate.

30 A solution of ethyl 4-acetyl-7-chloro-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine-2-carboxylate in tetrahydrofuran is added dropwise to a stirred suspension of lithium aluminum hydride in ethyl ether to give 7-chloro-4-ethyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine-2-methanol.

EXAMPLE 28

35

7-Chloro-4-ethyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde

Using the general procedure of Example 3, replacing 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol with 7-chloro-4-ethyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine-2-methanol, prepared as in Example 27, gives 7-chloro-4-ethyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde.

EXAMPLE 2945 7-Chloro-3,4,5,6-tetrahydro-2-methylthieno[4,3,2-ef][3]benzazepine and 7-Chloro-3,4,5,6-tetrahydro-2-methyl-4-(2-propenyl)thieno[4,3,2-ef][3]benzazepine

Using the general procedure of Example 26, replacing ethyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate with 7-chloro-3,4,5,6-tetrahydro-2,4-dimethylthieno[4,3,2-ef][3]benzazepine, prepared as in Example 12, gives 7-chloro-3,4,5,6-tetrahydro-2-methylthieno[4,3,2-ef][3]benzazepine.

A solution of 7-chloro-3,4,5,6-tetrahydro-2-methylthieno[4,3,2-ef][3]benzazepine in dry acetone is treated with potassium carbonate and allyl iodide to give 7-chloro-3,4,5,6-tetrahydro-2-methyl-4-(2-propenyl)thieno[4,3,2-ef][3]benzazepine.

55

EXAMPLE 30Ethyl 3,4,5,6-Tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate

5 A mixture of ethyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate hydrochloride, prepared as in Example 1, and platinum oxide in absolute ethanol is shaken under hydrogen to give ethyl 3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate hydrochloride.

EXAMPLE 31

10

Ethyl 3,4,5,6-Tetrahydro-4-methyl-7-nitrothieno[4,3,2-ef][3]benzazepine-2-carboxylate

A solution of ethyl 3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate hydrochloride, prepared as in Example 30, in sulfuric acid is stirred at 0 °C and treated with 70% nitric acid to give ethyl 3,4,5,6-tetrahydro-4-methyl-7-nitrothieno[4,3,2-ef][3]benzazepine-2-carboxylate.

EXAMPLE 32Ethyl 7-Amino-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate

20

Using the general procedure of Example 12, replacing 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol hydrochloride with ethyl 3,4,5,6-tetrahydro-4-methyl-7-nitrothieno[4,3,2-ef][3]benzazepine-2-carboxylate, prepared as in Example 31, gives ethyl 7-amino-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate.

25

EXAMPLE 33Ethyl 7-Dimethylamino-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate

30

A mixture of ethyl 3,4,5,6-tetrahydro-4-methyl-7-nitrothieno[4,3,2-ef][3]benzazepine-2-carboxylate, prepared as in Example 31, 37% formalin and platinum oxide in absolute ethanol is shaken under hydrogen to give ethyl 7-dimethylamino-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate.

EXAMPLE 34

35

Ethyl 7-Fluoro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate, 7-Fluoro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol, and 7-Fluoro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde

40

Using the general procedure of Example 1, replacing 4-chlorothiophenol with 4-fluorothiophenol gives ethyl 7-fluoro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate.

Using the general procedure of Example 2, replacing ethyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate with ethyl 7-fluoro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate gives 7-fluoro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol.

45

Using the general procedure of Example 3, replacing 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol with 7-fluoro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol gives 7-fluoro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde.

50

EXAMPLE 353,4,5,6-Tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol

55

Using the general procedure of Example 2, replacing ethyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate with ethyl 3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate, prepared as in Example 30, gives 3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol hydrochloride.

EXAMPLE 36Ethyl 7-Bromo-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate

5 Using the general procedure of Example 1, replacing 4-chlorothiophenol with 4-bromothiophenol gives ethyl 7-bromo-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate.

EXAMPLE 37

10 Ethyl 7,9-Dichloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate

Using the general procedure of Example 1, replacing 4-chlorothiophenol with 2,4-dichlorothiophenol yields ethyl 7,9-dichloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate hydrochloride.

15

EXAMPLE 38

Ethyl 7-Cyano-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate, 7-Cyano-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol, and
 20 7-Cyano-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde

Ethyl 7-bromo-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine 2-carboxylate, prepared as in Example 36, is heated with cuprous cyanide in dimethylformamide to give ethyl 7-cyano-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate.

25

Using the general procedure of Example 22, replacing ethyl 7-chloro-4-ethoxycarbonyl-3,4,5,6-tetrahydrothieno[4,3,2-ef][3]benzazepine-2-carboxylate with ethyl 7-cyano-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate gives 7-cyano-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol.

30

Using the general procedure of Example 3, replacing 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol with 7-cyano-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol gives 7-cyano-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde.

EXAMPLE 39

35 Ethyl 9-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate, 9-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol, and
9-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde

40 Using the general of procedure of Example 34, replacing 4-fluorothiophenol with 2-chlorothiophenol gives ethyl 9-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate, 9-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol and 9-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde.

EXAMPLE 40

45

7-Chloro-3,4,5,6-tetrahydro-N,N,4-trimethylthieno[4,3,2-ef][3]benzazepine-2-sulfonamide

7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine, prepared as in Example 11, is treated with excess chlorosulfonic acid and the mixture is carefully poured into ice water and carefully treated with dimethylamine to give 7-chloro-3,4,5,6-tetrahydro-N,N,4-trimethylthieno[4,3,2-ef][3]benzazepine-2-sulfonamide.

50

EXAMPLE 41

55 Diethyl (7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-yl)phosphonate

2-Bromo-7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine, prepared as in Example 23, is treated with butyllithium in ethyl ether and then with diethyl chlorophosphate to give diethyl (7-chloro-

3,4,5,6-tetrahydro-4-methylthieno-[4,3,2-ef][3]benzazepine-2-yl)phosphonate.

EXAMPLE 42

5 7-Chloro-3,4,5,6-tetrahydro-4-methyl-2-(methylthio)thieno[4,3,2-ef][3]benzazepine

A solution of 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine (0.7 g, 3 mmol) in tetrahydrofuran (40 ml) was stirred at -78 °C and treated with butyllithium in tetrahydrofuran (2.5N, 1.8 ml, 4.5 mmol) to give 7-chloro-3,4,5,6-tetrahydro-2-lithio-4-methylthieno[4,3,2-ef][3]benzazepine.

10 A solution of 7-chloro-3,4,5,6-tetrahydro-2-lithio-4-methylthieno[4,3,2-ef][3]benzazepine was treated with a solution of methyl disulfide (0.75 g, 8 mmol) in tetrahydrofuran (10 ml). The mixture was allowed to warm to 25 °C, stirred for 30 minutes, treated with water and extracted with ethyl ether. The organic phase was dried with magnesium sulfate, concentrated in vacuo and the residue dissolved in ethyl ether and treated with hydrogen chloride to give 0.35 g (37%) of 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-(methylthio)thieno-
15 [4,3,2-ef][3]benzazepine hydrochloride: mp 220 °C (d).

EXAMPLE 43

20 7-Chloro-3,4,5,6-tetrahydro-4-methyl-2-(phenyl)thieno[4,3,2-ef][3]benzazepine

Using the general procedure of Example 42, replacing methyl disulfide with tributyltin chloride, gave tributyl-[2-(7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin-2-yl)]stannane.

A solution of tributyl-[2-(7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin-2-yl)] stannane (0.27 g, 0.5 mmol) and iodobenzene (0.1 g, 0.5 mmol) in tetrahydrofuran (25 ml) was treated with bis-
25 (triphenylphosphine)palladium(II) chloride (19 mg) and heated to reflux for 48 hours. The mixture was treated with water, extracted with ethyl ether and the organic phase was dried with magnesium sulfate and concentrated in vacuo. The residue was chromatographed on a preparative silica gel plate eluted with ethyl ether-hexane (2:1) to give an oil. The oil was dissolved in ethyl ether and treated with hydrogen chloride to give 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-(phenyl)thieno[4,3,2-ef][3]benzazepine hydrochloride.
30

EXAMPLE 44

7-Chloro-3,4,5,6-tetrahydro- α ,4-dimethylthieno[4,3,2-ef][3]benzazepine-2-methanol

35 Sodium borohydride (0.2 g, 5 mmol) was added to a solution of 2-acetyl-7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine, prepared as in Example 10, (0.2 g, 0.7 mmol) in methanol (30 ml) stirred at 0 °C. The mixture was stirred for 2 hours, diluted with water and extracted with ethyl ether. The organic phase was dried with magnesium sulfate and concentrated in vacuo to give 7-chloro-3,4,5,6-tetrahydro- α ,4-dimethylthieno[4,3,2-ef][3]benzazepine-2-methanol: mp 167-168 °C.
40

EXAMPLE 45

7-Chloro-3,4,5,6-tetrahydro- α , α -4-trimethylthieno[4,3,2-ef][3]benzazepine-2-methanol

45 Methylmagnesium bromide in tetrahydrofuran (3M, 5 ml, 45 mmol) was added to a solution of ethyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate, prepared as in Example 1, (3.09 g, 10 mmol) in tetrahydrofuran (60 ml) stirred under argon. The mixture was stirred for 1 hour, treated with saturated aqueous ammonium chloride and extracted with ethyl ether. The organic phase was dried with magnesium sulfate and concentrated in vacuo to give an oil which was chromatographed on silica gel
50 eluted with methanol-methylene chloride (1:10) to give 1 g of 7-chloro-3,4,5,6-tetrahydro- α , α -4-trimethylthieno[4,3,2-ef][3]benzazepine-2-methanol: mp 250 °C.

EXAMPLE 46

55 7-Chloro-2-[[4-(chlorophenyl)methoxy]methyl]-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine

Using the general procedure of Example 19, replacing allyl iodide with 4-chlorobenzyl chloride gives 7-chloro-2-[[4-(chlorophenyl)methoxy]methyl]-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine hy-

drochloride.

EXAMPLE 47

5 7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxamide

Using the general procedure of Example 7, replacing dimethylamine with ammonia, gave 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxamide: mp 203-204 ° C.

10 EXAMPLE 48

7-Chloro-3,4,5,6-tetrahydro-4-methyl-2-(1-methylethyl)thieno[4,3,2-ef][3]benzazepine

15 Triethylamine (2 ml) and methanesulfonyl chloride (1.1 g, 10 mmol) were added to a solution of 7-chloro-3,4,5,6-tetrahydro- $\alpha,\alpha,4$ -trimethylthieno[4,3,2-ef][3]benzazepine-2-methanol, prepared as in Example 45, (0.7 g, 2.3 mmol) in methylene chloride (50 ml) stirred at 0 ° C. The mixture was stirred for 3 hours, diluted with water and basified with 10% aqueous sodium hydroxide. The organic phase was dried with magnesium sulfate and concentrated in vacuo to give an oil. The oil was dissolved in ethyl ether and treated with ethereal hydrogen chloride to give 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-(1-methylethenyl)-
20 thieno[4,3,2-ef][3]benzazepine hydrochloride: mp 203-205 ° C (d).

Using the general procedure of Example 13, replacing 7-chloro-2-ethenyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine hydrochloride with 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-(1-methylethenyl)thieno[4,3,2-ef][3]benzazepine hydrochloride, gave 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-(1-methylethyl)thieno[4,3,2-ef][3]benzazepine: mp 225 ° C.

25

EXAMPLE 49

7-Chloro-3,4,5,6-tetrahydro-4-methyl-2-(propyl)thieno[4,3,2-ef][3]benzazepine

30 Using the general procedure of Example 13, replacing methyltriphenylphosphonium bromide with ethyltriphenylphosphonium bromide gave 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-(propyl)thieno[4,3,2-ef][3]benzazepine hydrochloride: mp 144-145 ° C.

EXAMPLE 50

35

2,7-Dichloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine

40 Using the general procedures of Example 1, Method B, iii, v and vi, replacing carbon dioxide with N-chlorosuccinimide, gave 2,7-dichloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine hydrochloride: mp 225 ° C.

EXAMPLE 51

45 An oral dosage form for administering the presently invented compounds is produced by screening, mixing, and filling into a hard gelatin capsule ingredients in the proportions shown in Table II, below.

Table II

Ingredients	Amounts
Ethyl 7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate	50 mg
magnesium stearate	5 mg
lactose	75 mg

55

EXAMPLE 52

The sucrose, calcium sulfate dihydrate and Formula (I) compound shown in Table III below, are mixed and granulated with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, screened and compressed into a tablet.

Table III

Ingredients	Amounts
Methyl 7-Chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate	100 mg
calcium sulfate dihydrate	150 mg
sucrose	20 mg
starch	10 mg
talc	5 mg
stearic acid	3 mg

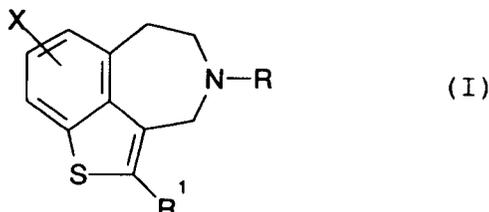
EXAMPLE 53

7-Chloro-3,4,5,6-tetrahydro-4-methyl-2-[(2-propenyloxy)methyl]thieno[4,3,2-ef][3]benzazepine, 75 mg, is dispersed in 25 ml of normal saline to prepare an injectable preparation.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound of the formula (I):



wherein

X is H, Cl, Br, F, I, CF₃, C₁₋₆alkyl, COR¹⁰, CO₂R¹⁰, CONR¹⁶R¹¹, CN, NO₂, NR¹²R¹³, OR¹², SC₁₋₄alkyl, S(CH₂)₀₋₆aryl, SCF₃, or any combination thereof of up to three substituents;

R is H, C₁₋₆alkyl, or C₃₋₅alkenyl;

R¹ is W, (CH₂)₀₋₂CWYZ, or C₃₋₅alkenyl, except where the double bond is in the 1-position;

R¹⁰ is C₁₋₆alkyl or (CH₂)₀₋₆aryl;

R¹¹ and R¹⁶ independently are H, C₁₋₆alkyl, or (CH₂)₀₋₆aryl;

R¹² is H, C₁₋₆alkyl, COR¹⁴, or SO₂R¹⁵;

each R¹³ independently is H or C₁₋₆alkyl;

R¹⁴ and R¹⁵ independently are C₁₋₆alkyl or (CH₂)₀₋₆aryl;

W is H, NO₂, C₁₋₆alkyl, CH₂CH₂OH, CN, C(R¹³)₂(OR²), CH₂OR², CH₂SR², COR², CO₂R², CONR³R⁴, SO₂NR³R⁴, SO₃R², SO₂R⁵, SOR⁵, SR⁵, P(O)(OR³)(OR⁴), P(O)R⁵(OR³), P(O)R⁵R⁶, P(O)-(OR²)NR³R⁴, P(O)(NR³R⁴)₂, P(O)R⁵(NR³R⁴), Cl, Br, F, I, CF₃, or (CH₂)₀₋₆aryl;

Y and Z independently are H or C₁₋₆alkyl;

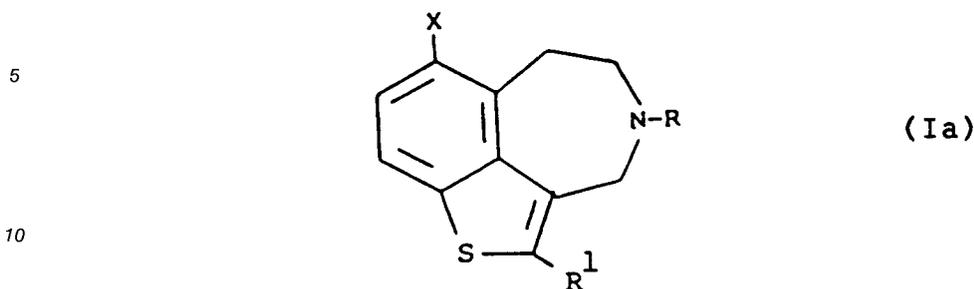
R², R³, and R⁴ independently are H, C₁₋₆alkyl, C₃₋₅alkenyl, or (CH₂)₀₋₆aryl;

R⁵ and R⁶ independently are C₁₋₆alkyl, C₃₋₅alkenyl, or (CH₂)₀₋₆aryl; and

aryl is a phenyl group which is unsubstituted or substituted by C₁₋₆alkyl, C₁₋₆alkoxy, halo, CF₃ or CN;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 of the formula (Ia):



wherein

- 15 X is H, Cl, Br, F, I, CF₃, C₁₋₆alkyl, COR¹⁰, CO₂R¹⁰, CONR¹⁶R¹¹, CN, NO₂, NR¹²R¹³, OR¹², SC₁₋₄alkyl, S(CH₂)₀₋₆aryl, or SCF₃;
 R is H, C₁₋₆alkyl, or C₃₋₅alkenyl;
 R¹ is W, (CH₂)₀₋₂CWYZ or C₃₋₅alkenyl, except where the double bond is in the 1-position;
 R¹⁰ is C₁₋₆alkyl or (CH₂)₀₋₆aryl;
 20 R¹¹ and R¹⁶ independently are H, C₁₋₆alkyl, or (CH₂)₀₋₆aryl,
 R¹² is H, C₁₋₆alkyl, COR¹⁴, or SO₂R¹⁵;
 each R¹³ independently is H or C₁₋₆alkyl;
 R¹⁴ and R¹⁵ independently are C₁₋₆alkyl or (CH₂)₀₋₆aryl;
 W is H, NO₂, C₁₋₆alkyl,
 25 CH₂CH₂OH, CN, C(R¹³)₂(OR²), CH₂SR², COR², CO₂R², CONR³R⁴, SO₂NR³R⁴, SO₃R², SO₂R⁵, SOR⁵, SR⁵, P(O)(OR³)(OR⁴), P(O)R⁵(OR³), P(O)R⁵R⁶, P(O)(OR²)NR³R⁴, P(O)(NR³R⁴)₂, P(O)R⁵(NR³R⁴), Cl, Br, F, I, CF₃, or (CH₂)₀₋₆aryl;
 Y and Z independently are H or C₁₋₆alkyl;
 R², R³, and R⁴ independently are H, C₁₋₆alkyl, C₃₋₅alkenyl, or (CH₂)₀₋₆aryl; and
 30 R⁵ and R⁶ independently are C₁₋₆alkyl, C₃₋₅alkenyl, or (CH₂)₀₋₆aryl; or a pharmaceutically acceptable salt thereof.

3. A compound according to either claim 1 or 2 wherein X is Cl, Br, F, or I.

- 35 4. A compound according to any one of claims 1 to 3 wherein R is CH₃.

5. A compound according to claim 4 which is 7-chloro-2-ethyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef]-[3]benzazepine, or a pharmaceutically acceptable salt thereof.

- 40 6. A compound according to claim 4 which is:

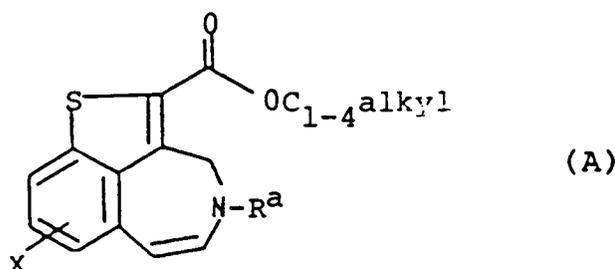
- ethyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate;
 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-methanol;
 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde;
 methyl 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate;
 45 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-[(2-propenyloxy)methyl]thieno[4,3,2-ef][3]benzazepine;
 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine;
 7-chloro-3,4,5,6-tetrahydro-2,4-dimethylthieno[4,3,2-ef][3]benzazepine;
 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-ethan-2-ol;
 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-ethan-2-one;
 50 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxamide;
 N,N-dimethyl-7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]-2-benzazepine-carboxamide;
 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-(1-methyl)ethylthieno[4,3,2-ef][3]benzazepine;
 7-chloro-2-propyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine; or
 2,7-dichloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine;
 55 or a pharmaceutically acceptable salt thereof.

7. A compound according to any one of claims 1 to 6 for use as a medicament.

8. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 7 and a pharmaceutically acceptable carrier.

9. A process for preparing a compound of the formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1, which comprises:

(a) reacting a compound of the formula (A):



wherein X is as defined in claim 1, and R^a is C_{1-6} alkyl, with an enamine reducing agent; and thereafter:

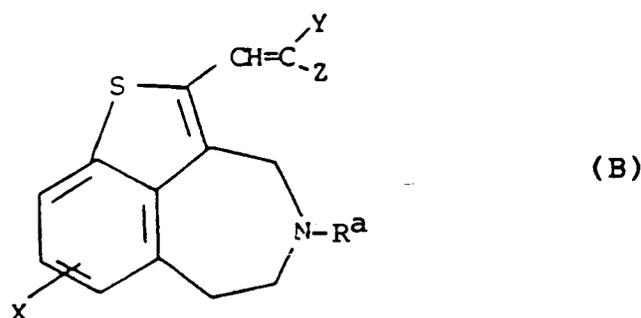
(i) for compounds in which R^1 is CH_2OH , reacting the formula (I) compound from above with an ester reducing agent, followed by:

- for compounds in which R^1 is CHO , reaction with an aldehyde-producing oxidant, or
- for compounds in which R^1 is CH_2 -halo or CH_2 -Y, reaction with a halogenating agent, optionally followed by displacement of the halide by a group Y selected from nitrogen, carbon, sulfur or phosphorous nucleophiles, or
- for compounds in which R^1 is CH_2OR^5 , reaction with a R^5 -halide, wherein R^5 is as defined in claim 1, in the presence of a base, or
- for compounds in which R^1 is CH_3 , reaction with an alcohol reducing agent; or

ii) for compounds in which R^1 is CO_2H , reacting the formula (I) compound from above with a hydrolytic reagent, followed by:

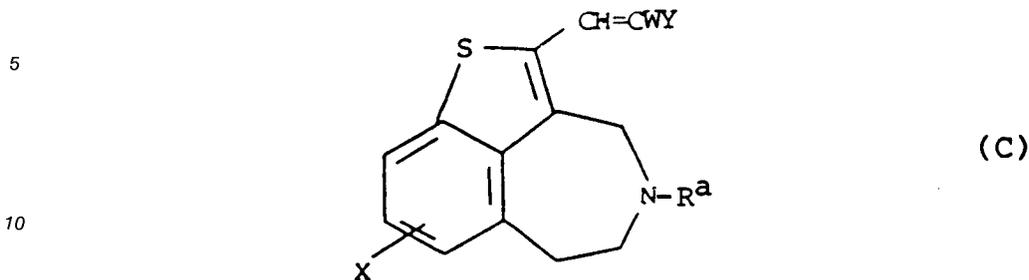
- for compounds in which R^1 is H or halo, reaction with a decarboxylating reagent, optionally followed by halogenation, or
- for compounds in which R^1 is $CONR^3R^4$, reaction with a halogenating agent followed by reaction with an amine HNR^3R^4 , wherein R^3 and R^4 are as defined in claim 1; or

(b) reacting a compound of the formula (B):



wherein X and R^a are as defined above, and Y and Z independently are H or C_{1-6} alkyl, with a vinyl reducing agent, or

(c) reacting a compound of the formula (C):



15 wherein X, W, and Y are as defined in claim 1 and R^a is as defined above, with a vinyl reducing agent, optionally followed by reacting the resulting formula (I) compound with a C_{1-6} alkyl-halo reagent in the presence of a base; and thereafter where necessary:

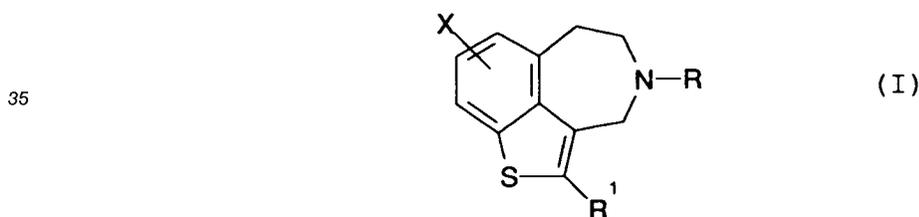
- converting a compound wherein R is methyl to the corresponding compound wherein R is H by reaction with an alkyl haloformate, followed by reaction with a reducing agent under acidic condition;
- converting a compound wherein R is H to the corresponding compound wherein R is C_{3-5} alkenyl by reaction with a halo $R^{7'}$ compound where $R^{7'}$ is C_{3-5} alkenyl; and
- forming a pharmaceutically acceptable salt thereof.

20

25 **10.** The use of a compound of the formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 in the manufacture of a medicament for the treatment of diseases in which α -adrenergic receptor antagonism is a factor.

Claims for the following Contracting States : ES, GR

30 **1.** A process for preparing a compound of the formula (I):



40 wherein

X is H, Cl, Br, F, I, CF_3 , C_{1-6} alkyl, COR^{10} , CO_2R^{10} , $CONR^{16}R^{11}$, CN, NO_2 , $NR^{12}R^{13}$, OR^{12} , SC_{1-4} alkyl, $S(CH_2)_{0-6}$ aryl, SCF_3 , or any combination thereof of up to three substituents;

R is H, C_{1-6} alkyl, or C_{3-5} alkenyl;

45 R^1 is W, $(CH_2)_{0-2}CWYZ$, or C_{3-5} alkenyl, except where the double bond is in the 1-position;

R^{10} is C_{1-6} alkyl or $(CH_2)_{0-6}$ aryl;

R^{11} and R^{16} independently are H, C_{1-6} alkyl, or $(CH_2)_{0-6}$ aryl;

R^{12} is H, C_{1-6} alkyl, COR^{14} , or SO_2R^{15} ;

each R^{13} independently is H or C_{1-6} alkyl;

50 R^{14} and R^{15} independently are C_{1-6} alkyl or $(CH_2)_{0-6}$ aryl;

W is H, NO_2 , C_{1-6} alkyl, CH_2CH_2OH , CN, $C(R^{13})_2(OR^2)$, CH_2SR^2 , COR^2 , CO_2R^2 , $CONR^3R^4$, $SO_2NR^3R^4$, SO_3R^2 , SO_2R^5 , SOR^5 , SR^5 , $P(O)(OR^3)(OR^4)$, $P(O)R^5(OR^3)$, $P(O)R^5R^6$, $P(O)(OR^2)NR^3R^4$, $P(O)(NR^3R^4)_2$, $P(O)R^5(NR^3R^4)$, Cl, Br, F, I, CF_3 , or $(CH_2)_{0-6}$ aryl;

Y and Z independently are H or C_{1-6} alkyl;

55 R^2 , R^3 , and R^4 independently are H, C_{1-6} alkyl, C_{3-5} alkenyl, or $(CH_2)_{0-6}$ aryl;

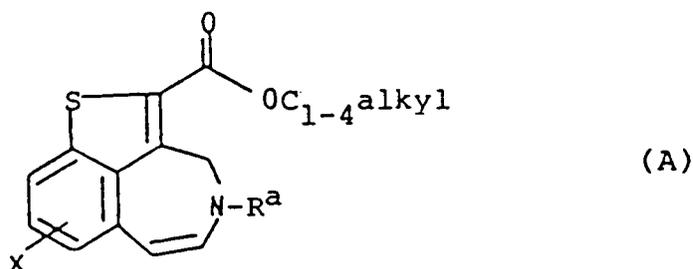
R^5 and R^6 independently are C_{1-6} alkyl, C_{3-5} alkenyl, or $(CH_2)_{0-6}$ aryl; and

aryl is a phenyl group which is unsubstituted or substituted by C_{1-6} alkyl, C_{1-6} alkoxy, halo, CF_3 or CN;

or a pharmaceutically acceptable salt thereof, which comprises:
 (a) reacting a compound of the formula (A):

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10



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wherein X is as hereinbefore defined and R^a is C₁₋₆ alkyl with an enamine reducing agent;
 and thereafter:

(i) for compounds in which R¹ is CH₂OH, reacting the formula (I) compound from above with an ester reducing agent, followed by:

20

- for compounds in which R¹ is CHO, reaction with an aldehyde-producing oxidant, or
- for compounds in which R¹ is CH₂-halo or CH₂-Y, reaction with a halogenating agent, optionally followed by displacement of the halide by a group Y selected from nitrogen, carbon, sulfur or phosphorous nucleophiles, or
- for compounds in which R¹ is CH₂OR⁵, reaction with a R⁵-halide, wherein R⁵ is as defined in claim 1, in the presence of a base, or

25

- for compounds in which R¹ is CH₃, reaction with an alcohol reducing agent; or

(ii) for compounds in which R¹ is CO₂H, reacting the formula (I) compound from above with a hydrolytic reagent, followed by:

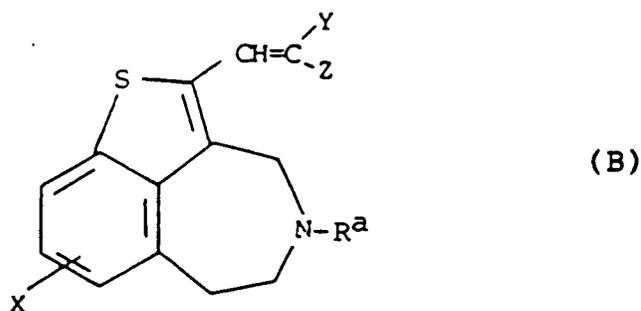
30

- for compounds in which R¹ is H or halo, reaction with a decarboxylating reagent, optionally followed by halogenation, or
- for compounds in which R¹ is CONR³R⁴, reaction with a halogenating agent, followed by reaction with an amine HNR³R⁴, wherein R³ and R⁴ are as defined in claim 1; or

(b) reacting a compound of the formula (B):

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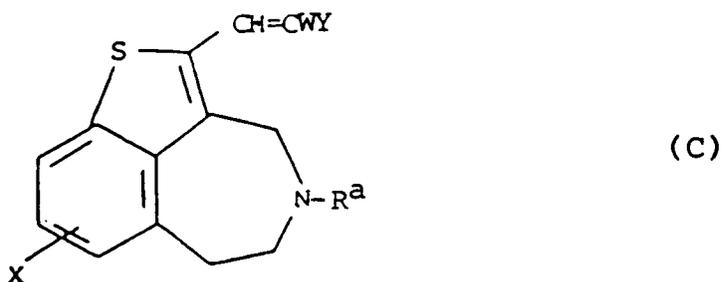
45

wherein X and R^a are as defined above, and Y and Z independently are H or C₁₋₆ alkyl, with a vinyl reducing agent, or

(c) reacting a compound of the formula (C):

50

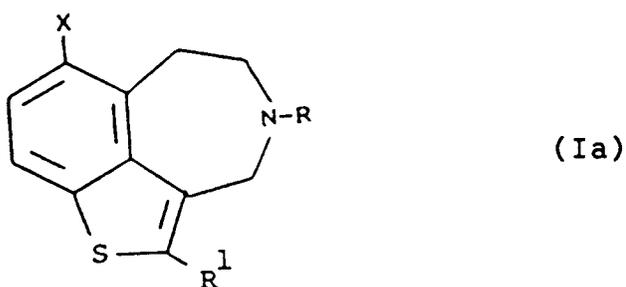
55



wherein X, W, R^a, and Y are as defined above, with a vinyl reducing agent, optionally followed by reacting the resulting formula (I) compound with a C₁₋₆ alkyl-halo reagent in the presence of a base; and thereafter where necessary:

- converting a compound wherein R is methyl to the corresponding compound wherein R is H by reaction with an alkyl haloformate followed by reaction with a reducing agent under acidic condition;
- converting a compound wherein R is H to the corresponding compound wherein R is C₃₋₅ alkenyl by reaction with a halo-R⁷ compound where R⁷ is C₃₋₅ alkenyl; and
- forming a pharmaceutically acceptable salt thereof.

2. A process for preparing a compound of claim 1 of the formula (Ia):



wherein

X is H, Cl, Br, F, I, CF₃, C₁₋₆ alkyl, COR¹⁰, CO₂R¹⁰, CONR¹⁶R¹¹, CN, NO₂, NR¹²R¹³, OR¹², SC₁₋₄ alkyl, S(CH₂)₀₋₆ aryl, or SCF₃;

R is H, C₁₋₆ alkyl, or C₃₋₅ alkenyl;

R¹ is W, (CH₂)₀₋₂CWYZ, or C₃₋₅ alkenyl, except where the double bond is in the 1-position;

R¹⁰ is C₁₋₆ alkyl or (CH₂)₀₋₆ aryl;

R¹¹ and R¹⁶ independently are H, C₁₋₆ alkyl, or (CH₂)₀₋₆ aryl;

R¹² is H, C₁₋₆ alkyl, COR¹⁴, or SO₂R¹⁵;

each R¹³ independently is H or C₁₋₆ alkyl;

R¹⁴ and R¹⁵ independently are C₁₋₆ alkyl or (CH₂)₀₋₆ aryl;

W is H, NO₂, C₁₋₆ alkyl, CH₂CH₂OH, CN, C(R¹³)₂(OR²), CH₂SR², COR², CO₂R², CONR³R⁴, SO₂NR³R⁴, SO₃R², SO₂R⁵, SOR⁵, SR⁵, P(O)(OR³)(OR⁴), P(O)R⁵(OR³), P(O)R⁵R⁶, P(O)(OR²)NR³R⁴, P(O)(NR³R⁴)₂, P(O)R⁵(NR³R⁴), Cl, Br, F, or CF₃, or (CH₂)₀₋₆ aryl;

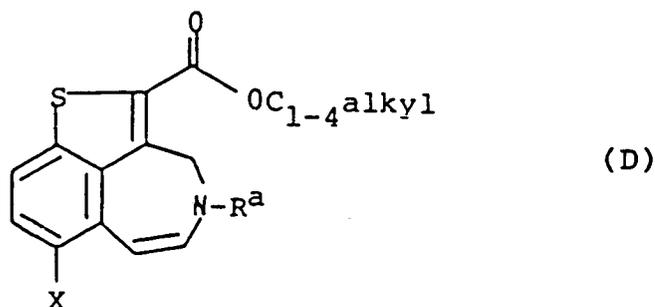
Y and Z independently are H or C₁₋₆ alkyl;

R², R³, and R⁴ independently are H, C₁₋₆ alkyl, C₃₋₅ alkenyl, or (CH₂)₀₋₆ aryl; and

R⁵ and R⁶ independently are C₁₋₆ alkyl, C₃₋₅ alkenyl, or (CH₂)₀₋₆ aryl; or a pharmaceutically acceptable salt thereof,

which comprises:

(a) reacting a compound of the formula (D):



wherein X is as defined in claim 1, and R^a is C₁₋₆ alkyl, with an enamine reducing agent; and thereafter:

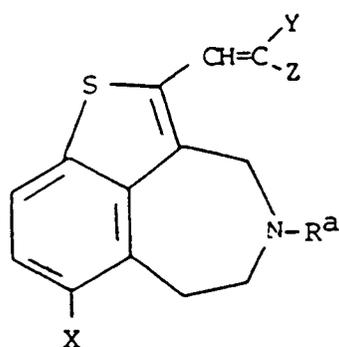
(i) for compounds in which R¹ is CH₂OH, reacting the formula (I) compound from above with an ester reducing agent, followed by:

- for compounds in which R¹ is CHO, reaction with an aldehyde-producing oxidant, or
- for compounds in which R¹ is CH₂-halo or CH₂-Y, reaction with a halogenating agent, optionally followed by displacement of the halide by group Y selected from a nitrogen, carbon, sulfur or phosphorous nucleophiles, or
- for compounds in which R¹ is CH₂OR⁵, reaction with a R⁵-halide, wherein R⁵ is as defined in claim 1, in the presence of a base, or
- for compounds in which R¹ is CH₃, reaction with an alcohol reducing agent; or

(ii) for compounds in which R¹ is CO₂H, reacting the formula (I) compound from above with a hydrolytic reagent, followed by:

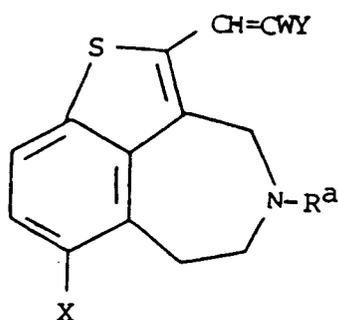
- for compounds in which R¹ is H or halo, reaction with a decarboxylating reagent, optionally followed by halogenation, or
- for compounds in which R¹ is CONR³R⁴, reaction with a halogenating agent, followed by reaction with an amine HNR³R⁴, wherein R³ and R⁴ are as defined in claim 1; or

(b) reacting a compound of the formula (E):



wherein X and R^a are as defined above, and X and Y independently are H or C₁₋₆ alkyl, with a vinyl reducing agent; or

(c) reacting a compound of the formula (F):



wherein X, W, R^a, and Y are as defined above, with a vinyl reducing agent, optionally followed by reacting the resulting formula (I) compound with a C₁₋₆ alkyl halo reagent in the presence of a base; and thereafter where necessary:

- converting a compound wherein R is methyl to the corresponding compound wherein R is H by reaction with an alkyl haloformate followed by reaction with a reducing agent under acidic condition;
- converting a compound wherein R is H to the corresponding compound wherein R is C₃₋₅ alkenyl by reaction with a halo-R⁷ compound where R⁷ is C₃₋₅ alkenyl, and
- forming a pharmaceutically acceptable salt thereof.

3. A process according to either claim 1 or claim 2 for preparing a compound wherein X is Cl, Br, F, or I.

4. A process according to any one of claims 1 to 3 for preparing a compound wherein R is CH₃.

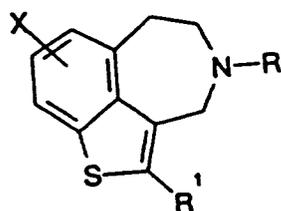
5. A process according to claim 4 for preparing a compound which is 7-chloro-2-ethyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine, or a pharmaceutically acceptable salt thereof.
6. A process according to claim 4 for preparing a compound which is:
- 5 ethyl-7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3] benzazepine-2-yl)-2-carboxylate;
 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-yl)-2-methanol;
 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxaldehyde;
 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-[(propenyloxy)methylthieno[4,3,2-ef][3]benzazepine;
 methyl chloro,3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxylate;
 10 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine;
 7-chloro-3,4,5,6-tetrahydro-2,4-dimethylthieno[4,3,2-ef][3]benzazepine;
 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-ethan-2-ol;
 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-ethan-2-one;
 7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine-2-carboxamide;
 15 N,N-dimethyl-7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]-2-benzazepine-carboxamide;
 7-chloro-3,4,5,6-tetrahydro-4-methyl-2-(1-methyl)ethylthieno[4,3,2-ef][3]benzazepine;
 7-chloro-2-propyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine; or
 2,7-dichloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine;
 or a pharmaceutically acceptable salt thereof.
- 20 7. A process for preparing 7-chloro-2-ethyl-2,3,4,5-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine or a pharmaceutically acceptable salt thereof which comprises reducing 7-chloro-2-ethenyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepine or a pharmaceutically acceptable salt thereof with hydrogen in the presence of a platinum or palladium catalyst on carbon.
- 25 8. A process for preparing a pharmaceutical composition which comprises bringing into association a compound of the formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 and a pharmaceutically acceptable carrier.
- 30 9. The use of a compound of the formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 in the manufacture of a medicament for the treatment of diseases in which α -adrenergic receptor antagonism is a factor.

Patentansprüche

35 **Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE,**

1. Verbindung der Formel (I):

40



(I)

45

wobei

50 X die Reste H, Cl, Br, F, I, CF₃, C₁₋₆-Alkyl, COR¹⁰, CO₂R¹⁰, CONR¹⁶R¹¹, CN, NO₂, NR¹²R¹³, OR¹², SC₁₋₄-Alkyl, S(CH₂)₀₋₆-Aryl, SCF₃ oder irgendeine Kombination davon mit bis zu 3 Substituenten darstellt;

R die Reste H, C₁₋₆-Alkyl oder C₃₋₅-Alkenyl darstellt;

R¹ die Reste W, (CH₂)₀₋₂CWYZ, oder C₃₋₅-Alkenyl, ausgenommen solche, bei denen die Doppelbindung in 1-Stellung ist, darstellt;

55 R¹⁰ die Reste C₁₋₆-Alkyl oder (CH₂)₀₋₆-Aryl darstellt;

R¹¹ und R¹⁶ unabhängig voneinander die Reste H, C₁₋₆-Alkyl oder (CH₂)₀₋₆-Aryl darstellen;

R¹² die Reste H, C₁₋₆-Alkyl, COR¹⁴ oder SO₂R¹⁵ darstellt;

jedes R¹³ unabhängig voneinander die Reste H oder C₁₋₆-Alkyl darstellt;

R¹⁴ und R¹⁵ unabhängig voneinander die Reste C₁₋₆-Alkyl oder (CH₂)₀₋₆-Aryl darstellen;
 W die Reste H, NO₂, C₁₋₆-Alkyl, CH₂CH₂OH, CN, C(R¹³)₂(OR²), CH₂OR², CH₂SR², COR², CO₂R²,
 CONR³R⁴, SO₂NR³R⁴, SO₃R², SO₂R⁵, SOR⁵, SR⁵, P(O)(OR³)(OR⁴), P(O)R⁵(OR³), P(O)R⁵R⁶, P(O)-
 (OR²)NR³R⁴, P(O)(NR³R⁴)₂, P(O)R⁵(NR³R⁴), Cl, Br, F, I, CF₃ oder (CH₂)₀₋₆-Aryl darstellt;

5 Y und Z unabhängig voneinander die Reste H oder C₁₋₆-Alkyl darstellen;

R², R³ und R⁴ unabhängig voneinander die Reste H, C₁₋₆-Alkyl, C₃₋₅-Alkenyl oder (CH₂)₀₋₆-Aryl darstellen;

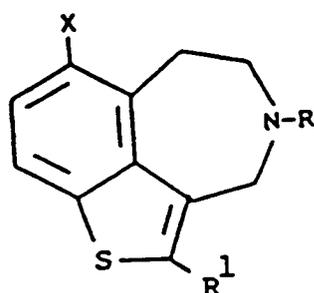
R⁵ und R⁶ unabhängig voneinander die Reste C₁₋₆-Alkyl, C₃₋₅-Alkenyl oder (CH₂)₀₋₆-Aryl darstellen;
 und

10 Aryl eine Phenylgruppe ist, welche unsubstituiert oder mit C₁₋₆-Alkyl, C₁₋₆-Alkoxy, Halogen, CF₃ oder CN substituiert ist;

oder ein pharmazeutisch verträgliches Salz davon.

2. Verbindung nach Anspruch 1 der Formel (Ia):

15



(Ia)

20

25

wobei

X die Reste H, Cl, Br, F, I, CF₃, C₁₋₆-Alkyl, COR¹⁰, CO₂R¹⁰, CONR¹⁶R¹¹, CN, NO₂, NR¹²R¹³, OR¹²,
 SC₁₋₄-Alkyl, S(CH₂)₀₋₆-Aryl oder SCF₃ darstellt;

30 R die Reste H, C₁₋₆-Alkyl oder C₃₋₅-Alkenyl darstellt;

R¹ die Reste W, (CH₂)₀₋₂CWYZ oder C₃₋₅-Alkenyl, ausgenommen solche, bei denen die Doppelbin-
 dung in 1-Stellung ist, darstellt;

R¹⁰ die Reste C₁₋₆-Alkyl oder (CH₂)₀₋₆-Aryl darstellt;

R¹¹ und R¹⁶ unabhängig voneinander die Reste H, C₁₋₆-Alkyl oder (CH₂)₀₋₆-Aryl darstellen;

35 R¹² die Reste H, C₁₋₆-Alkyl, COR¹⁴ oder SO₂R¹⁵ darstellt;

jedes R¹³ unabhängig voneinander die Reste H oder C₁₋₆-Alkyl darstellt;

R¹⁴ und R¹⁵ unabhängig voneinander die Reste C₁₋₆-Alkyl oder (CH₂)₀₋₆-Aryl darstellen;

W die Reste H, NO₂, C₁₋₆-Alkyl, CH₂CH₂OH, CN, C(R¹³)₂(OR²), CH₂SR², COR², CO₂R², CONR³R⁴,
 SO₂NR³R⁴, SO₃R², SO₂R⁵, SOR⁵, SR⁵, P(O)(OR³)(OR⁴), P(O)R⁵(OR³), P(O)R⁵R⁶, P(O)(OR²)NR³R⁴, P-
 (O)(NR³R⁴)₂, P(O)R⁵(NR³R⁴), Cl, Br, F, I, CF₃, oder (CH₂)₀₋₆-Aryl darstellt;

40

Y und Z unabhängig voneinander die Reste H oder C₁₋₆-Alkyl darstellen;

R², R³ und R⁴ unabhängig voneinander die Reste H, C₁₋₆-Alkyl, C₃₋₅-Alkenyl oder (CH₂)₀₋₆-Aryl darstellen; und

R⁵ und R⁶ unabhängig voneinander die Reste C₁₋₆-Alkyl, C₃₋₅-Alkenyl oder (CH₂)₀₋₆-Aryl darstellen,
 oder ein pharmazeutisch verträgliches Salz davon.

45

3. Verbindung nach Anspruch 1 oder 2, wobei X die Atome Cl, Br, F oder I darstellt.

4. Verbindung nach einem der Ansprüche 1 bis 3, wobei R eine CH₃-Gruppe darstellt.

50

5. Verbindung nach Anspruch 4, nämlich 7-Chlor-2-ethyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]-
 benzazepin oder ein pharmazeutisch verträgliches Salz davon.

6. Verbindung nach Anspruch 4, nämlich

55

7-Chlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin-2-carbonsäure-ethylester,

7-Chlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin-2-methanol,

7-Chlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin-2-carboxaldehyd;

7-Chlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin-2-carbonsäure-methylester,

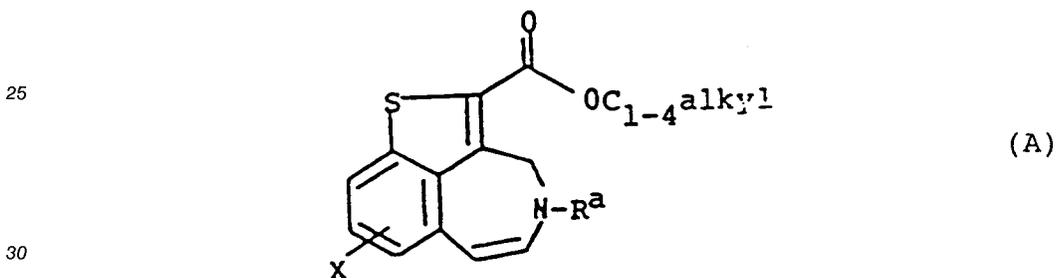
7-Chlor-3,4,5,6-tetrahydro-4-methyl-2-[(2-propenyloxy)methyl]thieno[4,3,2-ef][3]benzazepin,
 7-Chlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin,
 7-Chlor-3,4,5,6-tetrahydro-2,4-dimethylthieno[4,3,2-ef][3]benzazepin,
 7-Chlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin-2-ethan-2-ol,
 5 7-Chlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin-2-ethan-2-on,
 7-Chlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin-2-carbonsäureamid,
 N,N-Dimethyl-7-chlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]-2-benzazepin-carbonsäureamid,
 7-Chlor-3,4,5,6-tetrahydro-4-methyl-2-(1-methyl)ethylthieno[4,3,2-ef][3]benzazepin,
 7-Chlor-2-propyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin oder
 10 2,7-Dichlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin oder
 ein pharmazeutisch verträgliches Salz davon.

7. Verbindung nach einem der Ansprüche 1 bis 6 zur Verwendung als Medikament.

15 8. Arzneimittel, das eine Verbindung nach einem der Ansprüche 1 bis 7 und einen pharmazeutisch verträglichen Träger umfaßt.

9. Verfahren zur Herstellung einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon gemäß Anspruch 1, welches umfaßt:

20 (a) Umsetzung einer Verbindung der Formel (A):



wobei X wie in Anspruch 1 definiert ist, und R^a einen C₁₋₆-Alkylrest bedeutet, mit einem Enamin-Reduktionsmittel;

35 und danach

(i) bei Verbindungen, in denen R¹ eine CH₂OH-Gruppe darstellt, Umsetzung der vorstehenden Verbindung der Formel (I) mit einem Ester-Reduktionsmittel, gefolgt von:

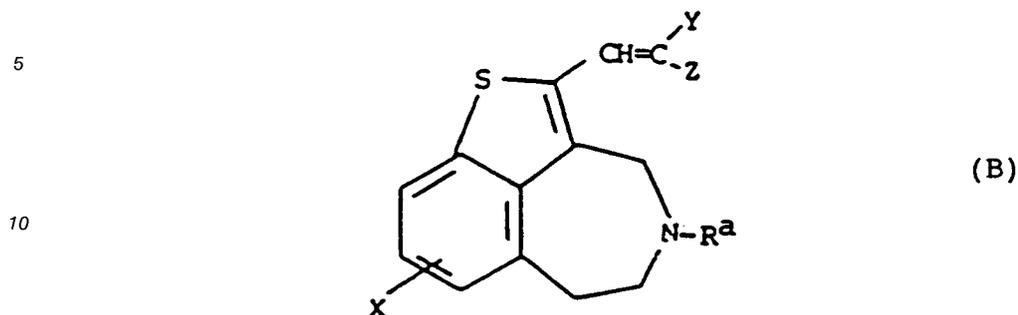
- bei Verbindungen, bei denen R¹ eine CHO-Gruppe darstellt, Umsetzung mit einem Aldehydliefernden Oxidationsmittel oder
- 40 - bei Verbindungen, in denen R¹ einen CH₂-Halogen- oder CH₂-Y-Rest darstellt, Umsetzung mit einem Halogenierungsmittel, gegebenenfalls gefolgt vom Ersatz des Halogenides durch eine Gruppe Y, die aus Stickstoff-, Kohlenstoff-, Schwefel- oder Phosphor-Nucleophilen ausgewählt wird, oder
- bei Verbindungen, in denen R¹ einen CH₂OR⁵-Rest darstellt, Umsetzung in Gegenwart einer Base mit einem R⁵-Halogenid, wobei R⁵ wie in Anspruch 1 definiert ist, oder
- 45 - bei Verbindungen, in denen R¹ eine CH₃-Gruppe darstellt, Umsetzung mit einem Alkohol-Reduktionsmittel; oder

(ii) bei Verbindungen, in denen R¹ eine CO₂H-Gruppe darstellt, Umsetzung der vorstehenden Verbindung der Formel (I) mit einem hydrolytisch wirkenden Reagens, gefolgt von:

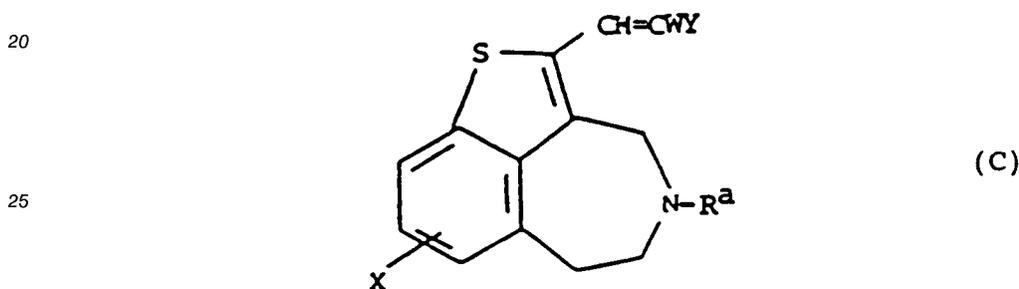
- 50 - bei Verbindungen, in denen R¹ ein H- oder Halogenatom darstellt, Umsetzung mit einem decarboxylierenden Reagens, gegebenenfalls gefolgt von einer Halogenierung oder
- bei Verbindungen, in denen R¹ den Rest CONR³R⁴ darstellt, Umsetzung mit einem Halogenierungsmittel, gefolgt von der Umsetzung mit einem Amin HNR³R⁴, wobei R³ und R⁴ wie in Anspruch 1 definiert sind; oder

55

(b) Umsetzung einer Verbindung der Formel (B):



15 wobei X und R^a wie vorstehend definiert sind, und Y und Z unabhängig voneinander die Reste H oder C₁₋₆-Alkyl darstellen, mit einem Vinyl-Reduktionsmittel, oder
(c) Umsetzung einer Verbindung der Formel (C):



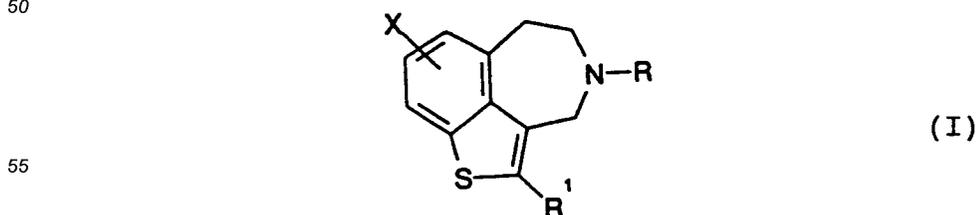
30 wobei X, W und Y wie in Anspruch 1 definiert sind, und R^a wie vorstehend definiert ist, mit einem Vinyl-Reduktionsmittel, gegebenenfalls gefolgt von einer Umsetzung der resultierenden Verbindung der Formel (I) mit einem C₁₋₆-Alkyl-Halogen-Reagens in Gegenwart einer Base; und danach, wo nötig:

- 35
- Überführen einer Verbindung, in der R eine Methylgruppe darstellt, in die entsprechende Verbindung, in der R ein H-Atom darstellt, durch Umsetzung mit einem Halogenameisensäure-alkylester, gefolgt von der Umsetzung mit einem Reduktionsmittel unter sauren Bedingungen;
 - Überführen einer Verbindung, in der R ein H-Atom darstellt, in die entsprechende Verbindung, in der R einen C₃₋₅-Alkenylrest darstellt, durch Umsetzung mit einer Halogen-R⁷-Verbindung, wobei R⁷ ein C₃₋₅-Alkenylrest ist; und
 - 40 - die Herstellung eines pharmazeutisch verträglichen Salzes davon.

10. Verwendung einer in Anspruch 1 definierten Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon bei der Herstellung eines Medikamentes zur Behandlung von Erkrankungen, bei denen ein adrenerger α-Rezeptor-Antagonismus eine Rolle spielt.

45 **Patentansprüche für folgende Vertragsstaaten : ES, GR**

1. Verfahren zur Herstellung einer Verbindung der Formel (I):



wobei

X die Reste H, Cl, Br, F, I, CF₃, C₁₋₆-Alkyl, COR¹⁰, CO₂R¹⁰, CONR¹⁶R¹¹, CN, NO₂, NR¹²R¹³, OR¹², SC₁₋₄-Alkyl, S(CH₂)₀₋₆-Aryl, SCF₃ oder irgendeine Kombination davon mit bis zu 3 Substituenten darstellt;

5 R die Reste H, C₁₋₆-Alkyl oder C₃₋₅-Alkenyl darstellt;

R¹ die Reste W, (CH₂)₀₋₂CWYZ, oder C₃₋₅-Alkenyl, ausgenommen solche, bei denen die Doppelbindung in 1-Stellung ist, darstellt;

R¹⁰ die Reste C₁₋₆-Alkyl oder (CH₂)₀₋₆-Aryl darstellt;

R¹¹ und R¹⁶ unabhängig voneinander die Reste H, C₁₋₆-Alkyl oder (CH₂)₀₋₆-Aryl darstellen;

10 R¹² die Reste H, C₁₋₆-Alkyl, COR¹⁴ oder SO₂R¹⁵ darstellt;

jedes R¹³ unabhängig voneinander die Reste H oder C₁₋₆-Alkyl darstellt;

R¹⁴ und R¹⁵ unabhängig voneinander die Reste C₁₋₆-Alkyl oder (CH₂)₀₋₆-Aryl darstellen;

W die Reste H, NO₂, C₁₋₆-Alkyl, CH₂CH₂OH, CN, C(R¹³)₂(OR²), CH₂SR², COR², CO₂R², CONR³R⁴, SO₂NR³R⁴, SO₃R², SO₂R⁵, SOR⁵, SR⁵, P(O)(OR³)(OR⁴), P(O)R⁵(OR³), P(O)R⁵R⁶, P(O)(OR²)NR³R⁴, P-

15 (O)(NR³R⁴)₂, P(O)R⁵(NR³R⁴), Cl, Br, F, I, CF₃ oder (CH₂)₀₋₆-Aryl darstellt;

Y und Z unabhängig voneinander die Reste H oder C₁₋₆-Alkyl darstellen;

R², R³ und R⁴ unabhängig voneinander die Reste H, C₁₋₆-Alkyl, C₃₋₅-Alkenyl oder (CH₂)₀₋₆-Aryl darstellen;

R⁵ und R⁶ unabhängig voneinander die Reste C₁₋₆-Alkyl, C₃₋₅-Alkenyl oder (CH₂)₀₋₆-Aryl darstellen;

20 und

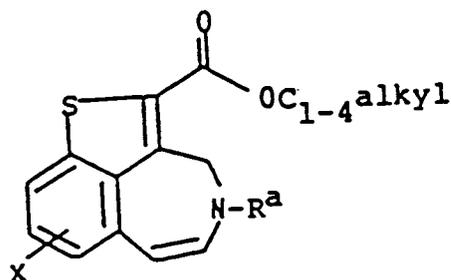
Aryl eine Phenylgruppe ist, welche unsubstituiert oder mit C₁₋₆-Alkyl, C₁₋₆-Alkoxy, Halogen, CF₃ oder CN substituiert ist;

oder eines pharmazeutisch verträglichen Salzes davon; welches umfaßt:

(a) Umsetzung einer Verbindung der Formel (A):

25

30



(A)

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wobei X wie vorstehend definiert ist, und R^a einen C₁₋₆-Alkylrest bedeutet, mit einem Enamin-Reduktionsmittel;

und danach

40

(i) für Verbindungen, in denen R¹ eine CH₂OH-Gruppe darstellt, Umsetzung der vorstehenden Verbindung der Formel (I) mit einem Ester-Reduktionsmittel, gefolgt von:

- bei Verbindungen, bei denen R¹ eine CHO-Gruppe darstellt, Umsetzung mit einem Aldehydliefernden Oxidationsmittel oder
- bei Verbindungen, in denen R¹ einen CH₂-Halogen- oder CH₂-Y-Rest darstellt, Umsetzung mit einem Halogenierungsmittel, gegebenenfalls gefolgt vom Ersatz des Halogenides durch eine Gruppe Y, die aus Stickstoff-, Kohlenstoff-, Schwefel- oder Phosphor-Nucleophilen ausgewählt wird, oder
- bei Verbindungen, in denen R¹ einen CH₂OR⁵-Rest darstellt, Umsetzung in Gegenwart einer Base mit einem R⁵-Halogenid, wobei R⁵ wie in Anspruch 1 definiert ist, oder
- bei Verbindungen, in denen R¹ eine CH₃-Gruppe darstellt, Umsetzung mit einem Alkohol-Reduktionsmittel; oder

45

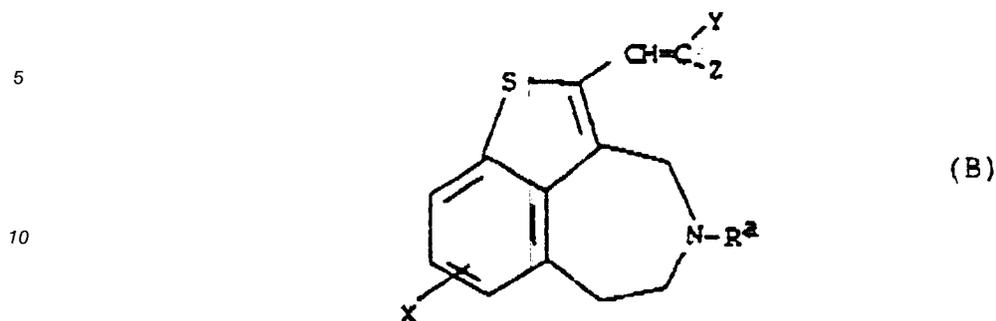
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(ii) bei Verbindungen, in denen R¹ eine CO₂H-Gruppe darstellt, Umsetzung der vorstehenden Verbindung der Formel (I) mit einem hydrolytisch wirkenden Reagens, gefolgt von:

- bei Verbindungen, in denen R¹ ein H- oder Halogenatom darstellt, Umsetzung mit einem decarboxylierenden Reagens, gegebenenfalls gefolgt von einer Halogenierung oder
- bei Verbindungen, in denen R¹ den Rest CONR³R⁴ darstellt, Umsetzung mit einem Halogenierungsmittel, gefolgt von der Umsetzung mit einem Amin HNR³R⁴, wobei R³ und R⁴ wie in Anspruch 1 definiert sind; oder

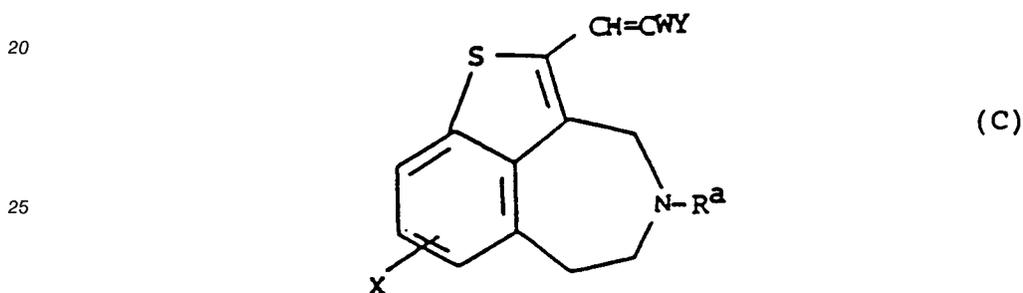
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(b) Umsetzung einer Verbindung der Formel (B):



15 wobei X und R^a wie vorstehend definiert sind, und Y und Z unabhängig voneinander die Reste H oder C₁₋₆-Alkyl darstellen, mit einem Vinyl-Reduktionsmittel, oder

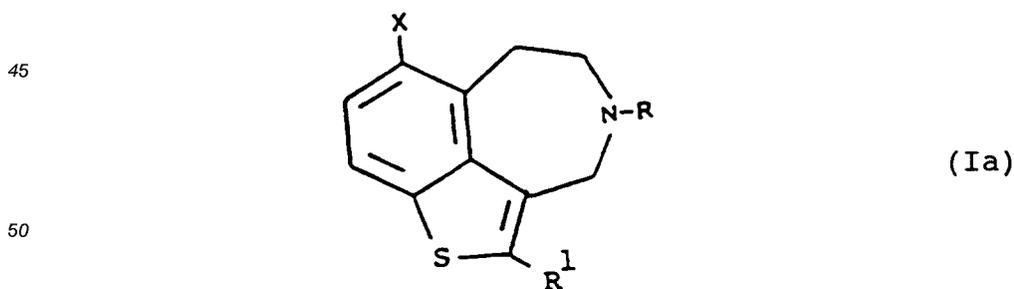
(c) Umsetzung einer Verbindung der Formel (C):



30 wobei X, W, R^a und Y wie vorstehend definiert sind, mit einem Vinyl-Reduktionsmittel, gegebenenfalls gefolgt von einer Umsetzung der resultierenden Verbindung der Formel (I) mit einem C₁₋₆-Alkyl-Halogen-Reagens in Gegenwart einer Base; und danach, wo nötig:

- 35
- Überführen einer Verbindung, in der R eine Methylgruppe darstellt, in die entsprechende Verbindung, in der R ein H-Atom darstellt, durch Umsetzung mit einem Halogenameisensäure-alkylester, gefolgt von der Umsetzung mit einem Reduktionsmittel unter sauren Bedingungen;
 - Überführen einer Verbindung, in der R ein H-Atom darstellt, in die entsprechende Verbindung, in der R einen C₃₋₅-Alkenylrest darstellt, durch Umsetzung mit einer Halogen-R⁷-Verbindung, wobei R⁷ ein C₃₋₅-Alkenylrest ist; und
 - Herstellung eines pharmazeutisch verträglichen Salzes davon.
- 40

2. Verfahren zur Herstellung einer Verbindung nach Anspruch 1 der Formel (Ia):



wobei

- 55
- X die Reste H, Cl, Br, F, I, CF₃, C₁₋₆-Alkyl, COR¹⁰, CO₂R¹⁰, CONR¹⁶R¹¹, CN, NO₂, NR¹²R¹³, OR¹², SC₁₋₄-Alkyl, S(CH₂)₀₋₆-Aryl oder SCF₃ darstellt;
 R die Reste H, C₁₋₆-Alkyl oder C₃₋₅-Alkenyl darstellt;
 R¹ die Reste W, (CH₂)₀₋₂CWYZ oder C₃₋₅-Alkenyl, ausgenommen solche, bei denen die Doppelbin-

5 dung in 1-Stellung ist, darstellt;

R^{10} die Reste C_{1-6} -Alkyl oder $(CH_2)_{0-6}$ -Aryl darstellt;

R^{11} und R^{16} unabhängig voneinander die Reste H, C_{1-6} -Alkyl oder $(CH_2)_{0-6}$ -Aryl darstellen;

R^{12} die Reste H, C_{1-6} -Alkyl, COR^{14} oder SO_2R^{15} darstellt;

5 jedes R^{13} unabhängig voneinander die Reste H oder C_{1-6} -Alkyl darstellt;

R^{14} und R^{15} unabhängig voneinander die Reste C_{1-6} -Alkyl oder $(CH_2)_{0-6}$ -Aryl darstellen;

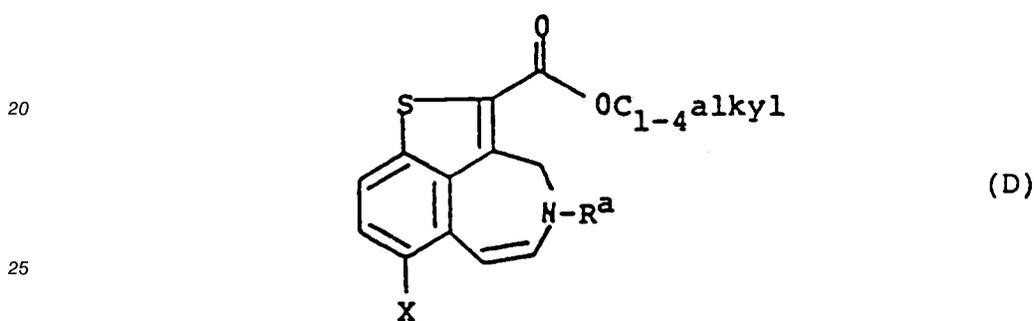
W die Reste H, NO_2 , C_{1-6} -Alkyl, CH_2CH_2OH , CN, $C(R^{13})_2(OR^2)$, CH_2SR^2 , COR^2 , CO_2R^2 , $CONR^3R^4$, $SO_2NR^3R^4$, SO_3R^2 , SO_2R^5 , SOR^5 , SR^5 , $P(O)(OR^3)(OR^4)$, $P(O)R^5(OR^3)$, $P(O)R^5R^6$, $P(O)(OR^2)NR^3R^4$, $P(O)(NR^3R^4)_2$, $P(O)R^5(NR^3R^4)$, Cl, Br, F, CF_3 , oder $(CH_2)_{0-6}$ -Aryl darstellt;

10 Y und Z unabhängig voneinander die Reste H oder C_{1-6} -Alkyl darstellen;

R^2 , R^3 und R^4 unabhängig voneinander die Reste H, C_{1-6} -Alkyl, C_{3-5} -Alkenyl oder $(CH_2)_{0-6}$ -Aryl darstellen; und

R^5 und R^6 unabhängig voneinander die Reste C_{1-6} -Alkyl, C_{3-5} -Alkenyl oder $(CH_2)_{0-6}$ -Aryl darstellen, oder eines pharmazeutisch verträglichen Salzes davon, welches umfaßt:

15 (a) Umsetzung einer Verbindung der Formel (D):



wobei X wie in Anspruch 1 definiert ist, und R^a einen C_{1-6} -Alkylrest bedeutet, mit einem Enamin-Reduktionsmittel;

30

und danach

(i) bei Verbindungen, in denen R^1 eine CH_2OH -Gruppe darstellt, Umsetzung der vorstehenden Verbindung der Formel (I) mit einem Ester-Reduktionsmittel, gefolgt von:

35

- bei Verbindungen, bei denen R^1 eine CHO -Gruppe darstellt, Umsetzung mit einem Aldehydliefernden Oxidationsmittel oder
- bei Verbindungen, in denen R^1 einen CH_2 -Halogen- oder CH_2 -Y-Rest darstellt, Umsetzung mit einem Halogenierungsmittel, gegebenenfalls gefolgt vom Ersatz des Halogenides durch eine Gruppe Y, die aus Stickstoff-, Kohlenstoff-, Schwefel- oder Phosphor-Nucleophilen ausgewählt wird, oder
- bei Verbindungen, in denen R^1 einen CH_2OR^5 -Rest darstellt, Umsetzung in Gegenwart einer Base mit einem R^5 -Halogenid, wobei R^5 wie in Anspruch 1 definiert ist, oder
- bei Verbindungen, in denen R^1 eine CH_3 -Gruppe darstellt, Umsetzung mit einem Alkohol-Reduktionsmittel; oder

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(ii) bei Verbindungen, in denen R^1 eine CO_2H -Gruppe darstellt, Umsetzung der vorstehenden Verbindung der Formel (I) mit einem hydrolytisch wirkenden Reagens, gefolgt von:

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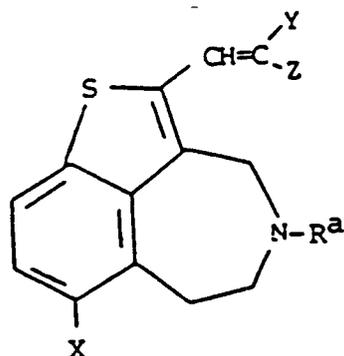
- bei Verbindungen, in denen R^1 ein H- oder Halogenatom darstellt, Umsetzung mit einem decarboxylierenden Reagens, gegebenenfalls gefolgt von einer Halogenierung oder
- bei Verbindungen, in denen R^1 den Rest $CONR^3R^4$ darstellt, Umsetzung mit einem Halogenierungsmittel, gefolgt von der Umsetzung mit einem Amin HNR^3R^4 , wobei R^3 und R^4 wie in Anspruch 1 definiert sind; oder

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(b) Umsetzung einer Verbindung der Formel (E):

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(E)

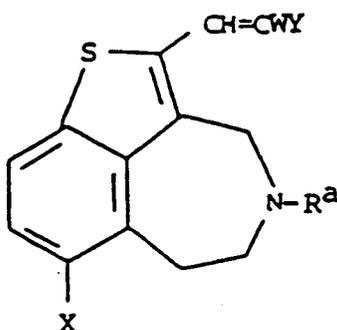
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wobei X und R^a wie vorstehend definiert sind, und X und Y unabhängig voneinander die Reste H oder C₁₋₆-Alkyl darstellen, mit einem Vinyl-Reduktionsmittel, oder

(c) Umsetzung einer Verbindung der Formel (F):

20



(F)

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wobei X, W, R^a und Y wie vorstehend definiert sind, mit einem Vinyl-Reduktionsmittel, gegebenenfalls gefolgt von einer Umsetzung der resultierenden Verbindung der Formel (I) mit einem C₁₋₆-Alkyl-Halogen-Reagens in Gegenwart einer Base; und danach, wo nötig:

35

- Überführen einer Verbindung, in der R eine Methylgruppe darstellt, in die entsprechende Verbindung, in der R ein H-Atom darstellt, durch Umsetzung mit einem Halogenameisensäurealkylester, gefolgt von der Umsetzung mit einem Reduktionsmittel unter sauren Bedingungen;
- Überführen einer Verbindung, in der R ein H-Atom darstellt, in die entsprechende Verbindung, in der R einen C₃₋₅-Alkenylrest darstellt, durch Umsetzung mit einer Halogen-R⁷-Verbindung, wobei R⁷ ein C₃₋₅-Alkenylrest ist; und
- Herstellung eines pharmazeutisch verträglichen Salzes davon.

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3. Verfahren nach Anspruch 1 oder 2 zur Herstellung einer Verbindung, bei der X die Atome Cl, Br, F oder I darstellt.

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4. Verfahren nach einem der Ansprüche 1 bis 3 zur Herstellung einer Verbindung, bei der R eine CH₃-Gruppe darstellt.

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5. Verfahren nach Anspruch 4, zur Herstellung von 7-Chlor-2-ethyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin oder eines pharmazeutisch verträglichen Salzes davon.

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6. Verfahren nach Anspruch 4, zur Herstellung von
 7-Chlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin-2-yl)-2-carbonsäure-ethylester,
 7-Chlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin-2-yl)-2-methanol,
 7-Chlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin-2-carboxaldehyd;
 7-Chlor-3,4,5,6-tetrahydro-4-methyl-2-[(propenyloxy)methyl]thieno[4,3,2-ef][3]benzazepin,
 Chlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin-2-carbonsäure-methylester,

7-Chlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin,
 7-Chlor-3,4,5,6-tetrahydro-2,4-dimethylthieno[4,3,2-ef][3]benzazepin,
 7-Chlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin-2-ethan-2-ol,
 7-Chlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin-2-ethan-2-on,
 5 7-Chlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin-2-carbonsäureamid,
 N,N-Dimethyl-7-chlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]-2-benzazepin-carbonsäureamid,
 7-Chlor-3,4,5,6-tetrahydro-4-methyl-2-(1-methyl)ethylthieno[4,3,2-ef][3]benzazepin,
 7-Chlor-2-propyl-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin oder
 2,7-Dichlor-3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin oder
 10 eines pharmazeutisch verträglichen Salzes davon.

7. Verfahren zur Herstellung von 7-Chlor-2-ethyl-2,3,4,5-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin
 oder eines pharmazeutisch verträglichen Salzes davon, das die Reduktion von 7-Chlor-2-ethenyl-
 3,4,5,6-tetrahydro-4-methylthieno[4,3,2-ef][3]benzazepin oder eines pharmazeutisch verträglichen Sal-
 zes davon mit Wasserstoff in der Gegenwart eines Platin- oder Palladiumkatalysators auf Kohlenstoff
 15 umfaßt.

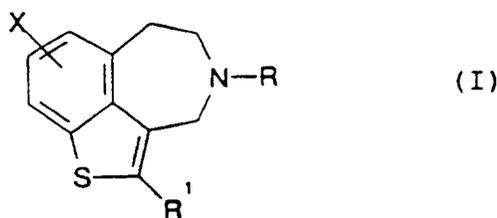
8. Verfahren zur Herstellung eines Arzneimittels, welches das Zusammenbringen einer Verbindung der
 Formel (I) oder eines pharmazeutisch verträglichen Salzes davon, gemäß Anspruch 1, und eines
 pharmazeutisch verträglichen Trägers umfaßt.
 20

9. Verwendung einer in Anspruch 1 definierten Verbindung der Formel (I) oder eines pharmazeutisch
 verträglichen Salzes davon bei der Herstellung eines Medikamentes zur Behandlung von Erkrankungen,
 bei denen ein adrenerger α -Rezeptor-Antagonismus eine Rolle spielt.
 25

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composé de formule (I):
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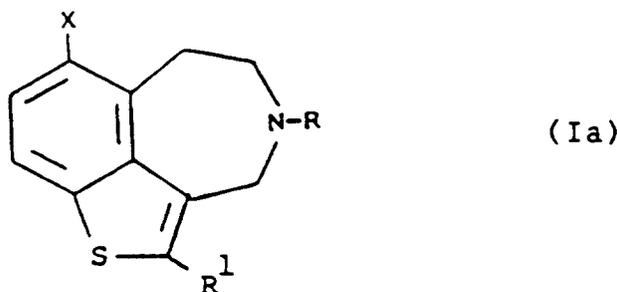


40 dans laquelle

- X représente H, Cl, Br, F, I, CF₃, un groupe alkyle C₁₋₆, COR¹⁰, COOR¹⁰, CONR¹⁶R¹¹, CN, NO₂, NR¹²R¹³, OR¹², S-alkyle C₁₋₄, S(CH₂)₀₋₆ aryle, SCF₃, ou toute combinaison de ceux-ci, allant jusqu'à trois substituants;
- R représente H, un groupe alkyle C₁₋₆, ou un groupe alkényle C₃₋₅;
- 45 - R¹ représente W, (CH₂)₀₋₂CWYZ, ou un groupe alkényle C₃₋₅ sauf là où la double liaison est en position 1
- R¹⁰ est un groupe alkyle C₁₋₆, ou un groupe (CH₂)₀₋₆ aryle;
- R¹¹ et R¹⁶, indépendamment, sont un atome d'hydrogène, un groupe alkyle C₁₋₆, ou un groupe (CH₂)₀₋₆ aryle;
- 50 - R¹² représente H, un groupe alkyle C₁₋₆, COR¹⁴, ou SO₂R¹⁵;
- chaque R¹³ est indépendamment, un atome d'hydrogène ou un groupe alkyle C₁₋₆;
- R¹⁴ et R¹⁵, indépendamment, sont un groupe alkyle C₁₋₆ ou un groupe (CH₂)₀₋₆ aryle;
- W représente H, NO₂, un groupe alkyle C₁₋₆, CH₂CH₂OH, CN, C(R¹³)₂(OR²), CH₂OR², CH₂SR², COR², COOR², CONR³R⁴, SO₂NR³R⁴, SO₃R², SO₂R⁵, SOR⁵, SR⁵, P(O)(OR³)(OR⁴), P(O)R⁵(OR³), P(O)R⁵R⁶, P(O)(OR²)NR³R⁴, P(O)(NR³R⁴)₂, P(O)R⁵(NR³R⁴), Cl, Br, F, I, CF₃, ou (CH₂)₀₋₆ aryle;
- 55 - Y et Z indépendamment, sont un atome d'hydrogène ou un groupe alkyle C₁₋₆;
- R², R³, et R⁴, indépendamment, sont un atome d'hydrogène, un groupe alkyle C₁₋₆, un groupe alkényle C₃₋₅, ou un groupe (CH₂)₀₋₆ aryle;

- R⁵ et R⁶, indépendamment, sont un groupe alkyle C₁₋₆, un groupe alkényle C₃₋₅, ou un groupe (CH₂)₀₋₆ aryle; et
 - aryle représente un groupe phényle non substitué, ou substitué par un groupe alkyle C₁₋₆, un groupe alcoxy C₁₋₆, un halo, un groupe CF₃ ou CN;
- ou un sel de celui-ci, acceptable du point de vue pharmaceutique.

2. Composé suivant la revendication 1, de formule (1a)



dans laquelle

- X représente H, Cl, Br, F, I, CF₃, un groupe alkyle C₁₋₆, COR¹⁰, COOR¹⁰, CONR¹⁶R¹¹, CN, NO₂, NR¹²R¹³, OR¹², S-alkyle C₁₋₄, S(CH₂)₀₋₆ aryle, ou SCF₃;
- R représente H, un groupe alkyle C₁₋₆, ou un groupe alkényle C₃₋₅;
- R¹ représente W, (CH₂)₀₋₂CWYZ, ou un groupe alkényle C₃₋₅ sauf là où la double liaison est en position 1
- R¹⁰ est un groupe alkyle C₁₋₆, ou un groupe (CH₂)₀₋₆ aryle;
- R¹¹ et R¹⁶, indépendamment, sont un atome d'hydrogène, un groupe alkyle C₁₋₆, ou un groupe (CH₂)₀₋₆ aryle;
- R¹² représente H, un groupe alkyle C₁₋₆, COR¹⁴, ou SO₂R¹⁵;
- chaque R¹³ est indépendamment, un atome d'hydrogène ou un groupe alkyle C₁₋₆;
- R¹⁴ et R¹⁵, indépendamment, sont un groupe alkyle C₁₋₆ ou un groupe (CH₂)₀₋₆ aryle;
- W représente H, NO₂, un groupe alkyle C₁₋₆, CH₂CH₂OH, CN, C(R¹³)₂(OR²), CH₂SR², COR², COOR², CONR³R⁴, SO₂NR³R⁴, SO₃R², SO₂R⁵, SOR⁵, SR⁵, P(O)(OR³)(OR⁴), P(O)R⁵(OR³), P(O)-R⁵R⁶, P(O)(OR²)NR³R⁴, P(O)(NR³R⁴)₂, P(O)R⁵(NR³R⁴), Cl, Br, F, I, CF₃, ou (CH₂)₀₋₆ aryle;
- Y et Z indépendamment, sont un atome d'hydrogène ou un groupe alkyle C₁₋₆;
- R², R³, et R⁴, indépendamment, sont un atome d'hydrogène, un groupe alkyle C₁₋₆, un groupe alkényle C₃₋₅, ou un groupe (CH₂)₀₋₆ aryle; et
- R⁵ et R⁶, indépendamment, sont un groupe alkyle C₁₋₆, un groupe alkényle C₃₋₅, ou un groupe (CH₂)₀₋₆ aryle;

ou un sel de celui-ci, acceptable du point de vue pharmaceutique.

3. Composé suivant la revendication 1 ou la revendication 2, dans lequel X représente Cl, Br, F, ou I.

4. Composé suivant l'une quelconque des revendications 1 à 3, dans lequel R est un groupe méthyle.

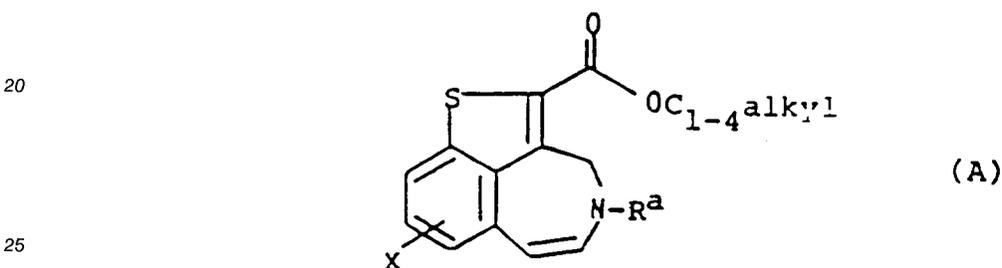
5. Composé suivant la revendication 4, qui est la 7-chloro-2-éthyl-3,4,5,6-tétrahydro-4-méthylthiéo-[4,3,2-ef][3]benzazépine, ou un sel de celle-ci, acceptable du point de vue pharmaceutique.

6. Composé suivant la revendication 4, qui est:

- le 7-chloro-3,4,5,6-tétrahydro-4-méthylthiéo-[4,3,2-ef][3]benzazépine-2-carboxylate d'éthyle;
- le 7-chloro-3,4,5,6-tétrahydro-4-méthylthiéo-[4,3,2-ef][3]benzazépine-2-méthanol;
- le 7-chloro-3,4,5,6-tétrahydro-4-méthylthiéo-[4,3,2-ef][3]benzazépine-2-carboxaldéhyde;
- le 7-chloro-3,4,5,6-tétrahydro-4-méthylthiéo-[4,3,2-ef][3]benzazépine-2-carboxylate de méthyle;
- le 7-chloro-3,4,5,6-tétrahydro-4-méthyl-2-[(2-propényloxy)méthyl]thiéo-[4,3,2-ef][3]benzazépine;
- la 7-chloro-3,4,5,6-tétrahydro-4-méthylthiéo-[4,3,2-ef][3]benzazépine;
- la 7-chloro-3,4,5,6-tétrahydro-2,4-diméthylthiéo-[4,3,2-ef][3]benzazépine;
- le 7-chloro-3,4,5,6-tétrahydro-4-méthylthiéo-[4,3,2-ef][3]benzazépine-2-éthan-2-ol;
- la 7-chloro-3,4,5,6-tétrahydro-4-méthylthiéo-[4,3,2-ef][3]benzazépine-2-éthan-2-one;

- le 7-chloro-3,4,5,6-tétrahydro-4-méthylthiéno-[4,3,2-ef][3]benzazépine-2-carboxamide;
 - le N,N-diméthyl-7-chloro-3,4,5,6-tétrahydro-4-méthylthiéno-[4,3,2-ef][3]-2-benzazépine-carboxamide;
 - la 7-chloro-3,4,5,6-tétrahydro-4-méthyl-2-(1-méthyl)éthylthiéno-[4,3,2-ef][3]benzazépine;
 - la 7-chloro-2-propyl-3,4,5,6-tétrahydro-4-méthylthiéno-[4,3,2-ef][3]benzazépine; ou
 - la 2,7-dichloro-3,4,5,6-tétrahydro-4-méthylthiéno-[4,3,2-ef][3]benzazépine;
- ou un sel de celui-ci, acceptable du point de vue pharmaceutique.

7. Composé suivant l'une quelconque des revendications 1 à 6, pour l'utilisation comme médicament.
8. Composition pharmaceutique qui comprend un composé suivant l'une quelconque des revendications 1 à 7 et un véhicule, acceptable du point de vue pharmaceutique.
9. Procédé de préparation d'un composé de formule (I), ou d'un sel de celui-ci, acceptable du point de vue pharmaceutique, tel que défini dans la revendication 1, qui comprend:
- (a) la réaction d'un composé de formule (A):

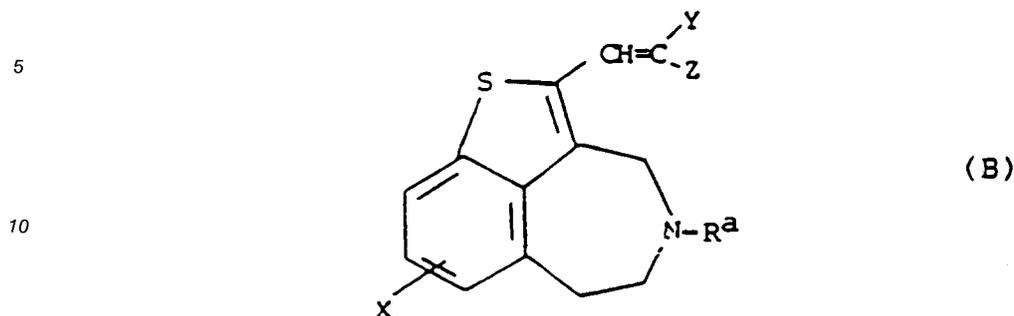


dans laquelle X est tel que défini dans la revendication 1, et R^a est un groupe alkyle C₁₋₆, avec un agent èneamine réducteur;

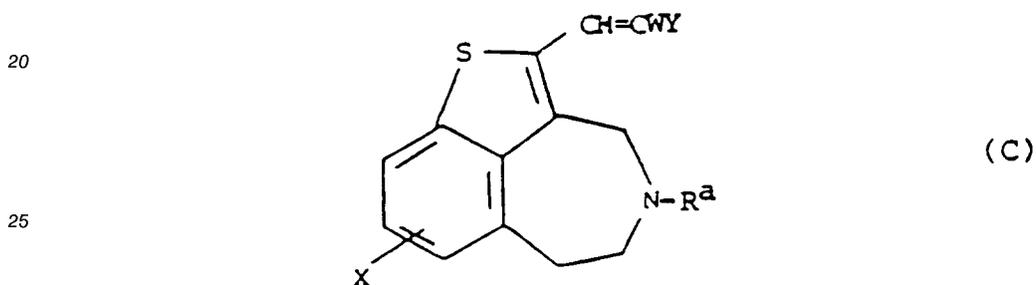
et ensuite:

- (i) pour les composés dans lesquels R¹ représente CH₂OH, la réaction du composé de formule (I) qui en découle, avec un agent ester réducteur, suivie:
- pour les composés dans lesquels R¹ représente CHO, de la réaction avec un oxydant générateur d'aldéhyde, ou,
 - pour les composés dans lesquels R¹ représente CH₂-halo, ou CH₂-Y, de la réaction avec un agent halogénant, suivie éventuellement du déplacement de l'halogénure par un groupe Y, choisi parmi les nucléophiles azotés, carbonés, soufrés ou phosphorés.
- ou
- pour les composés dans lesquels R¹ représente CH₂OR⁵, de la réaction avec un R⁵-halogénure, dans lequel R⁵ est tel que défini dans la revendication 1, en présence d'une base, ou
 - pour les composés dans lesquels R¹ représente CH₃, de la réaction avec un agent alcool réducteur; ou
- (ii) pour les composés dans lesquels R¹ représente COOH, la réaction du produit de formule (I) ci-dessus, avec un agent hydrolytique, suivie:
- pour les composés dans lesquels R¹ représente H ou un halogène, de la réaction avec un agent de décarboxylation, suivie éventuellement d'une halogénéation, ou
 - pour les composés dans lesquels R¹ représente CONR³R⁴, de la réaction avec un agent d'halogénéation, suivie de la réaction avec une amine HNR³R⁴, dans laquelle R³ et R⁴ sont tels que définis dans la revendication 1; ou

(b) la réaction d'un composé de formule (B):



15 dans laquelle X et R^a sont tels que définis plus haut, et Y et Z, indépendamment, représentent un atome d'hydrogène ou un groupe alkyle C₁₋₆, avec un agent vinyl réducteur, ou
 (c) la réaction d'un composé de formule (C):



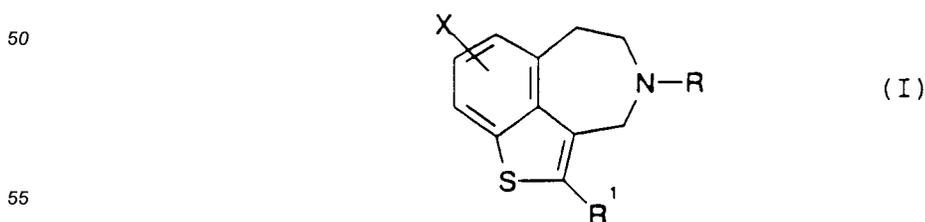
30 dans laquelle X, W, et Y sont tels que définis dans la revendication 1 et R^a est tel que défini plus haut, avec un agent vinyl réducteur, suivie éventuellement de la réaction du produit de formule (I) obtenu, avec un réactif alkyle C₁₋₆ halo, en présence d'une base; et ensuite, si nécessaire:

- la conversion d'un composé dans lequel R est un groupe méthyle, en composé correspondant dans lequel R est un atome d'hydrogène, par réaction avec un haloformiate d'alkyle, suivie de la réaction avec un agent réducteur dans des conditions acides;
- la conversion d'un composé dans lequel R est un atome d'hydrogène, en composé correspondant dans lequel R est un groupe alkényle C₃₋₅, par réaction avec un composé halo-R^{7'} dans lequel R^{7'} est un groupe alkényle C₃₋₅; et
- la formation d'un sel de celui-ci, acceptable du point de vue pharmaceutique.

40 **10.** Utilisation d'un composé de formule (I) ou d'un sel de celui-ci, acceptable du point de vue pharmaceutique, tel que défini dans la revendication 1, dans la fabrication d'un médicament pour le traitement de maladies dans lesquelles l'antagonisme des récepteurs alpha-adrénergiques constitue un facteur.

45 **Revendications pour les Etats contractants suivants : ES, GR**

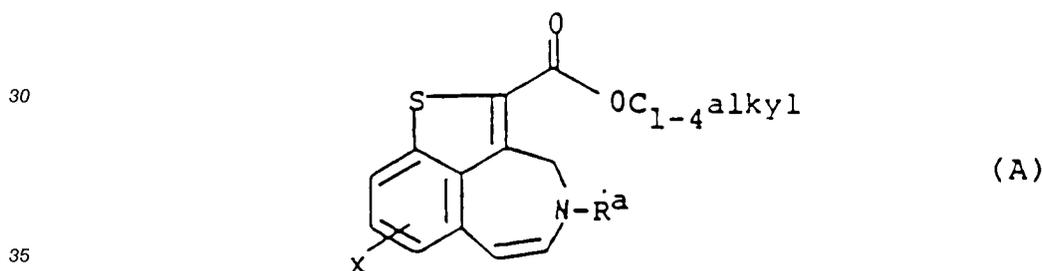
1. Procédé de préparation d'un composé de formule (I)



dans laquelle

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- X représente H, Cl, Br, F, I, CF₃, un groupe alkyle C₁₋₆, COR¹⁰, COOR¹⁰, CONR¹⁶R¹¹, CN, NO₂, NR¹²R¹³, OR¹², S-alkyle C₁₋₄, S(CH₂)₀₋₆ aryle, SCF₃, ou toute combinaison de ceux-ci, allant jusqu'à trois substituants;
 - R représente H, un groupe alkyle C₁₋₆, ou un groupe alkènyle C₃₋₅;
 - 5 - R¹ représente W, (CH₂)₀₋₂CWYZ, ou un groupe alkènyle C₃₋₅ sauf là où la double liaison est en position 1
 - R¹⁰ est un groupe alkyle C₁₋₆, ou un groupe (CH₂)₀₋₆ aryle;
 - R¹¹ et R¹⁶, indépendamment, sont un atome d'hydrogène, un groupe alkyle C₁₋₆, ou un groupe (CH₂)₀₋₆ aryle;
 - 10 - R¹² représente H, un groupe alkyle C₁₋₆, COR¹⁴, ou SO₂R¹⁵;
 - chaque R¹³ est indépendamment, un atome d'hydrogène ou un groupe alkyle C₁₋₆;
 - R¹⁴ et R¹⁵, indépendamment, sont un groupe alkyle C₁₋₆ ou un groupe (CH₂)₀₋₆ aryle;
 - W représente H, NO₂, un groupe alkyle C₁₋₆, CH₂CH₂OH, CN, C(R¹³)₂(OR²), CH₂SR², COR², COOR², CONR³R⁴, SO₂NR³R⁴, SO₃R², SO₂R⁵, SOR⁵, SR⁵, P(O)(OR³)(OR⁴), P(O)R⁵(OR³), P(O)-R⁵R⁶, P(O)(OR²)NR³R⁴, P(O)(NR³R⁴)₂, P(O)R⁵(NR³R⁴), Cl, Br, F, I, CF₃, ou (CH₂)₀₋₆ aryle;
 - 15 - Y et Z indépendamment, sont un atome d'hydrogène ou un groupe alkyle C₁₋₆;
 - R², R³, et R⁴, indépendamment, sont un atome d'hydrogène, un groupe alkyle C₁₋₆, un groupe alkènyle C₃₋₅, ou un groupe (CH₂)₀₋₆ aryle;
 - R⁵ et R⁶, indépendamment, sont un groupe alkyle C₁₋₆, un groupe alkènyle C₃₋₅, ou un groupe (CH₂)₀₋₆ aryle; et
 - 20 - aryle représente un groupe phényle non substitué, ou substitué par un groupe alkyle C₁₋₆, un groupe alcoxy C₁₋₆, un halo, un groupe CF₃ ou CN;
- ou un sel de celui-ci, acceptable du point de vue pharmaceutique, qui comprend:
- 25 (a) la réaction d'un composé de formule (A):



dans laquelle X est tel que défini plus haut, et R^a est un groupe alkyle C₁₋₆, avec un agent èneamine réducteur;

40 et ensuite:

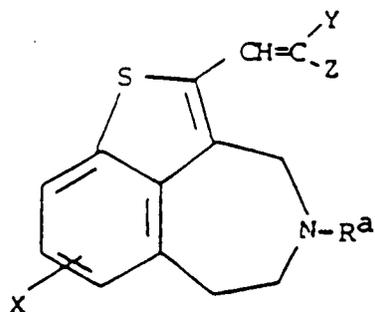
- (i) pour les composés dans lesquels R¹ représente CH₂OH, la réaction du composé de formule (I) qui en découle, avec un agent ester réducteur, suivie:
- pour les composés dans lesquels R¹ représente CHO, de la réaction avec un oxydant générateur d'aldéhyde, ou,
 - 45 • pour les composés dans lesquels R¹ représente CH₂-halo, ou CH₂-Y, de la réaction avec un agent d'halogénéation, suivie éventuellement du déplacement de l'halogénure par un groupe Y, choisi parmi les nucléophiles azotés, carbonés, soufrés, ou phosphorés,
 - ou
 - 50 • pour les composés dans lesquels R¹ représente CH₂OR⁵, de la réaction avec un R⁵-halogénure, dans lequel R⁵ est tel que défini dans la revendication 1, en présence d'une base, ou
 - pour les composés dans lesquels R¹ représente CH₃, de la réaction avec un agent alcool réducteur; ou
- (ii) pour les composés dans lesquels R¹ représente COOH, la réaction du produit de formule (I) ci-dessus, avec un agent hydrolytique, suivie:
- 55 • pour les composés dans lesquels R¹ représente H ou un halogène, de la réaction avec un agent de décarboxylation, suivie éventuellement d'une halogénéation, ou

- pour les composés dans lesquels R¹ représente CONR³R⁴, de la réaction avec un agent d'halogénéation, suivie de la réaction avec une amine HNR³R⁴, dans laquelle R³ et R⁴ sont tels que définis dans la revendication 1; ou
- (b) la réaction d'un composé de formule (B):

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(B)

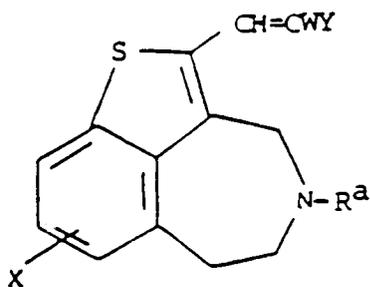
dans laquelle X et R^a sont tels que définis plus haut, et Y et Z, indépendamment, représentent un atome d'hydrogène ou un groupe alkyle C1-6, avec un agent vinyl réducteur, ou

(c) la réaction d'un composé de formule (C):

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(C)

dans laquelle X, W, R^a, et Y sont tels que définis plus haut, avec un agent vinyl réducteur, suivie éventuellement de la réaction du produit de formule (I) obtenu, avec un réactif alkyle C₁₋₆ halo, en présence d'une base;

et ensuite, si nécessaire:

35

40

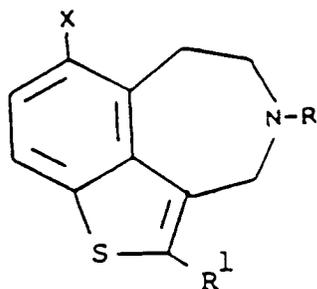
- la conversion d'un composé dans lequel R est un groupe méthyle, en composé correspondant dans lequel R est un atome d'hydrogène, par réaction avec un haloformiate d'alkyle, suivie de la réaction avec un agent réducteur dans des conditions acides;
- la conversion d'un composé dans lequel R est un atome d'hydrogène, en composé correspondant dans lequel R est un groupe alkényle C₃₋₅, par réaction avec un composé halo-R⁷ dans lequel R⁷ est un groupe alkényle C₃₋₅; et
- la formation d'un sel de celui-ci, acceptable du point de vue pharmaceutique.

45

2. Procédé de préparation d'un composé suivant la revendication 1, de formule (1a):

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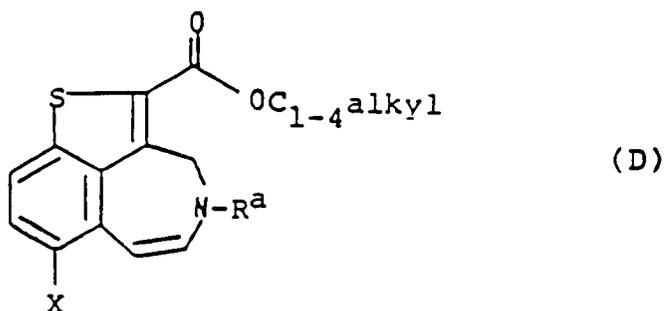


(1a)

dans laquelle

- X représente H, Cl, Br, F, I, CF₃, un groupe alkyle C₁₋₆, COR¹⁰, COOR¹⁰, CONR¹⁶R¹¹, CN, NO₂, NR¹²R¹³, OR¹², S-alkyle C₁₋₄, S(CH₂)₀₋₆ aryle, ou SCF₃;
 - R représente H, un groupe alkyle C₁₋₆, ou un groupe alkènyle C₃₋₅;
 - R¹ représente W, (CH₂)₀₋₂CWYZ, ou un groupe alkènyle C₃₋₅ sauf là où la double liaison est en position 1
 - R¹⁰ est un groupe alkyle C₁₋₆, ou un groupe (CH₂)₀₋₆ aryle;
 - R¹¹ et R¹⁶, indépendamment, sont un atome d'hydrogène, un groupe alkyle C₁₋₆, ou un groupe (CH₂)₀₋₆ aryle;
 - R¹² représente H, un groupe alkyle C₁₋₆, COR¹⁴, ou SO₂R¹⁵;
 - chaque R¹³ est indépendamment, un atome d'hydrogène ou un groupe alkyle C₁₋₆;
 - R¹⁴ et R¹⁵, indépendamment, sont un groupe alkyle C₁₋₆ ou un groupe (CH₂)₀₋₆ aryle;
 - W représente H, NO₂, un groupe alkyle C₁₋₆, CH₂CH₂OH, CN, C(R¹³)₂(OR²), CH₂SR², COR², COOR², CONR³R⁴, SO₂NR³R⁴, SO₃R², SO₂R⁵, SOR⁵, SR⁵, P(O)(OR³)(OR⁴), P(O)R⁵(OR³), P(O)-R⁵R⁶, P(O)(OR²)NR³R⁴, P(O)(NR³R⁴)₂, P(O)R⁵(NR³R⁴), Cl, Br, F, I, ou CF₃, ou (CH₂)₀₋₆ aryle;
 - Y et Z indépendamment, sont un atome d'hydrogène ou un groupe alkyle C₁₋₆;
 - R², R³, et R⁴, indépendamment, sont un atome d'hydrogène, un groupe alkyle C₁₋₆, un groupe alkènyle C₃₋₅, ou un groupe (CH₂)₀₋₆ aryle; et
 - R⁵ et R⁶, indépendamment, sont un groupe alkyle C₁₋₆, un groupe alkènyle C₃₋₅, ou un groupe (CH₂)₀₋₆ aryle;
- ou un sel de celui-ci, acceptable du point de vue pharmaceutique, qui comprend:

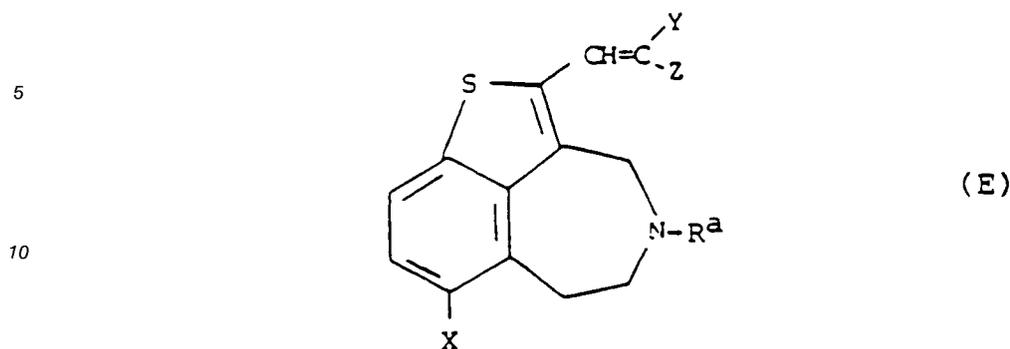
(a) la réaction d'un composé de formule (D):



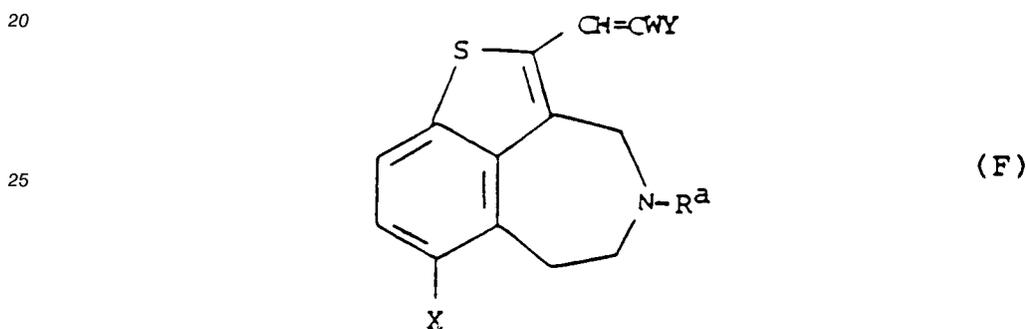
dans laquelle X est tel que défini dans la revendication 1, et R^a est un groupe alkyle C₁₋₆, avec un agent èneamine réducteur; et ensuite:

- (i) pour les composés dans lesquels R¹ représente CH₂OH, la réaction du composé de formule (I) qui en découle, avec un agent ester réducteur, suivie:
 - pour les composés dans lesquels R¹ représente CHO, de la réaction avec un oxydant générateur d'aldéhyde, ou,
 - pour les composés dans lesquels R¹ représente CH₂-halo, ou CH₂-Y, de la réaction avec un agent d'halogénéation, suivie éventuellement du déplacement de l'halogénure par un groupe Y, choisi parmi les nucléophiles azotés, carbonés, soufrés, ou phosphorés,
 - ou
 - pour les composés dans lesquels R¹ représente CH₂OR⁵, de la réaction avec un R⁵-halogénure, dans lequel R⁵ est tel que défini dans la revendication 1, en présence d'une base, ou
 - pour les composés dans lesquels R¹ représente CH₃, de la réaction avec un agent alcool réducteur; ou
- (ii) pour les composés dans lesquels R¹ représente COOH, la réaction du produit de formule (I) ci-dessus, avec un agent hydrolytique, suivie:
 - pour les composés dans lesquels R¹ représente H ou un halogène, de la réaction avec un agent de décarboxylation, suivie éventuellement d'une halogénéation, ou
 - pour les composés dans lesquels R¹ représente CONR³R⁴, de la réaction avec un agent d'halogénéation, suivie de la réaction avec une amine HNR³R⁴, dans laquelle R³ et R⁴ sont tels que définis dans la revendication 1; ou

(b) la réaction d'un composé de formule (E):



15 dans laquelle X et R^a sont tels que définis plus haut, et Y et Z, indépendamment, représentent un atome d'hydrogène ou un groupe alkyle C_{1-6} , avec un agent vinyl réducteur, ou
 (c) la réaction d'un composé de formule (F):



30 dans laquelle X, W, R^a , et Y sont tels que définis plus haut, avec un agent vinyl réducteur, suivie éventuellement de la réaction du produit de formule (I) obtenu, avec un réactif alkyle C_{1-6} halo, en présence d'une base;

35 et ensuite, si nécessaire:

- la conversion d'un composé dans lequel R est un groupe méthyle, en composé correspondant dans lequel R est un atome d'hydrogène, par réaction avec un haloformiate d'alkyle, suivie de la réaction avec un agent réducteur dans des conditions acides;
- la conversion d'un composé dans lequel R est un atome d'hydrogène, en composé correspondant dans lequel R est un groupe alkényle C_{3-5} , par réaction avec un composé halo- R^7 dans lequel R^7 est un groupe alkényle C_{3-5} ; et
- la formation d'un sel de celui-ci, acceptable du point de vue pharmaceutique.

40 3. Procédé suivant la revendication 1 ou la revendication 2, de préparation d'un composé dans lequel X représente Cl, Br, F, ou I.

45 4. Procédé suivant l'une quelconque des revendications 1 à 3, de préparation d'un composé dans lequel R est un groupe méthyle.

50 5. Procédé suivant la revendication 4, de préparation d'un composé qui est la 7-chloro-2-éthyl-3,4,5,6-tétrahydro-4-méthylthiéo[4,3,2-ef][3]benzazépine, ou un sel de celle-ci, acceptable du point de vue pharmaceutique.

55 6. Procédé suivant la revendication 4, de préparation d'un composé qui est:

- le 7-chloro-3,4,5,6-tétrahydro-4-méthylthiéo-[4,3,2-ef][3]benzazépine-2-carboxylate d'éthyle;
- le 7-chloro-3,4,5,6-tétrahydro-4-méthylthiéo-[4,3,2-ef][3]benzazépine-2-méthanol;
- le 7-chloro-3,4,5,6-tétrahydro-4-méthylthiéo-[4,3,2-ef][3]benzazépine-2-carboxaldehyde;
- le 7-chloro-3,4,5,6-tétrahydro-4-méthyl-2-[(2-propényloxy)méthyl]thiéo-[4,3,2-ef][3]benzazépine;

- le 7-chloro-3,4,5,6-tétrahydro-4-méthylthiéno-[4,3,2-ef][3]benzazépine-2-carboxylate de méthyle;
 - la 7-chloro-3,4,5,6-tétrahydro-4-méthylthiéno-[4,3,2-ef][3]benzazépine;
 - la 7-chloro-3,4,5,6-tétrahydro-2,4-diméthylthiéno-[4,3,2-ef][3]benzazépine;
 - le 7-chloro-3,4,5,6-tétrahydro-4-méthylthiéno-[4,3,2-ef][3]benzazépine-2-éthan-2-ol;
 - 5 - la 7-chloro-3,4,5,6-tétrahydro-4-méthylthiéno-[4,3,2-ef][3]benzazépine-2-éthan-2-one;
 - le 7-chloro-3,4,5,6-tétrahydro-4-méthylthiéno-[4,3,2-ef][3]benzazépine-2-carboxamide;
 - le N,N-diméthyl-7-chloro-3,4,5,6-tétrahydro-4-méthylthiéno-[4,3,2-ef][3]-2-benzazépine-carboxamide;
 - la 7-chloro-3,4,5,6-tétrahydro-4-méthyl-2-(1-méthyl)éthylthiéno-[4,3,2-ef][3]benzazépine-;
 - 10 - la 7-chloro-2-propyl-3,4,5,6-tétrahydro-4-méthylthiéno-[4,3,2-ef][3]benzazépine; ou
 - la 2,7-dichloro-3,4,5,6-tétrahydro-4-méthylthiéno-[4,3,2-ef][3]benzazépine;
- ou un sel de celui-ci, acceptable du point de vue pharmaceutique.

7. Procédé de préparation de la 7-chloro-2-éthyl-2,3,4,5-tétrahydro-4-méthylthiéno-[4,3,2-ef][3]-benzazépine, ou un sel de celle-ci, acceptable du point de vue pharmaceutique, qui comprend la
- 15 réduction de la 7-chloro-2-éthényl-3,4,5,6-tétrahydro-4-méthylthiéno-[4,3,2-ef][3]benzazépine, ou d'un sel de celle-ci, acceptable du point de vue pharmaceutique, par l'hydrogène en présence d'un catalyseur à base de platine ou de palladium sur charbon.
- 20 8. Procédé de préparation d'une composition pharmaceutique qui comprend la mise en association d'un composé de formule (I), ou d'un sel de celui-ci, acceptable du point de vue pharmaceutique, tel que défini dans la revendication 1, avec un véhicule acceptable du point de vue pharmaceutique.
9. Utilisation d'un composé de formule (I) ou d'un sel de celui-ci, acceptable du point de vue pharmaceutique, tel que défini dans la revendication 1, dans la fabrication d'un médicament pour le traitement de
- 25 maladies dans lesquelles l'antagonisme des récepteurs alpha-adrénergiques constitue un facteur.

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